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PREFACE

The Surgical Laboratories of the Department of Surgery, College of Physicians and Surgeons, New York City, were organized in 1903 by Dr. Joseph A. Blake then Professor of Surgery, with the encouragement of a former professor of the College, Dr. William T. Bull. Articles have been published from time to time by the various investigators working in these laboratories, reprints of which have been bound in book form. Volume i of this series includes the reprints of articles published from 1903 to 1907; volume ii, 1907-1917; volume iii, 1918-1920. From 1914 Dr. George E. Brewer was Professor of Surgery and later Dr. Adrian V. S. Lambert acted as such until Dr. Allen O. Whipple was appointed in 1921. This present volume iv includes reprints of publications from 1920 until 1927.

A glance over the articles reveals that in them the changing mode of thought of the surgeon has been closely paralleled. The men in the eighties and nineties of the last century felt that the operative procedure was all important, while the present day surgeon who brings the most to his patient is almost a physician interested in all specialties, all arts, all sciences.

Articles dealing largely with technique, it is true, are to be found in these volumes, but those dealing with biology, with embryology, with physiology, with bacteriology, with immunity and with physical chemistry are numerous. Attention is called to the wide range of interest of the investigators and particularly to their industry.

Personal observations of the actual work from 1903 to the present, of the care of the laboratory, the specimens, the apparatus and of the animals has shown convincingly how ideal all must be, particularly the surgical technique employed, in order to warrant conducting such experiments. Similarly there have been those who have carefully reviewed the efforts of others and who have given much thought to their own attempts. These men were striving to know what happened, what were the factors involved, rather than either to disprove others or to approve their own theories. Apparently those with the widest interests and those who were aware that many others were contributors to the accuracy of their own observations, of happenings in their individual experiments, were the most constructive. And the worth of any attempt could never be foretold; for almost always valuable observations accrued which were far aside from the "plan" of the investigator. In fact, in teaching the medical students who have passed through the College of Physicians and Surgeons during these years, it is hard to evaluate the information traceable to the efforts and products of these many ex-

perimenters. The articles found in these four volumes reveal but a fragment of the time and effort expended during these twenty-five years in the laboratory by students and by graduates, who never published their observations but surely carried away to their practice added experience in the art and science of surgery. As a consequence, the Laboratory, the College and medicine is deeply indebted to all who have given so freely of their time and effort. Therefore, appreciation is here expressed for what they have accomplished, well knowing the satisfaction so many of them have derived from their work.

The readings made by man by means of his many marvelous instruments of precision focussed upon happenings in every field of science, all his observations made through the ages, assayed by the modes of thought which have been nurtured by philosophy and reassayed by mathematics, declare against a *status quo* and inevitably in favor of continuous change. All is happenings; all is change—happenings; functions—never thing nor structure alone. This presages that the investigator in biology must be cautious if he leans too heavily upon statistics, upon records of things “discovered” upon “conclusions.” All those who count, measure and weigh, dealing in length, breadth and thickness must be cautious lest they forget that they probably live in a many dimensioned sphere of continuous happenings upon which they are attempting to fix a three dimensional hat that they have been taught to see. The investigator, therefore, must be aware that nothing is dead, but all is alive; he must be aware that he never sees a commencement nor an ending; he must be wholly aware that in such a many dimensioned arena no conclusions are possible. Thus all “events” with a commencement, an ending, are figments of the imagination in a hopeless effort to rationalize all human happenings, man’s evolution, his growth, his decay, his seeming structure. But, can segments of the eternal exist save in the imagination of man to whom events appear to be very much of life and of living?

Furthermore, in educational organizations, in experimental procedures as well as in other daily deeds, this conception of “events,” commencing and ending, leads to a mode of thought which moulds information and performance into distinctive building blocks. By means of thought employing these three dimensioned blocks, similar styles in architecture can result which in their essence appear unrelated. Thus man is able to conduct himself more comfortably in life, in experiments and in thoughts, seeming to believe concomitantly in most contradictory happenings and with the imaginary factors in nice cut and dried packages. Many observers believe in divers conceptions which to others seem to be diametrically opposed. So it is possible for many to disassociate

thought in the performance of daily procedures which appear to be in conflict. And furthermore always to make information more easily handled and more palatable, it is constantly undergoing subdivision. Thus upon education an increasing burden has been placed by its very self.

All happenings are related. All knowledge must be associated as it actually is in a single mass. In man's daily deeds, in his experiments, in his customs, in his unconscious thoughts, he must be as he is, involved with all people, with all things and not as his uppermost thoughts portray him to himself, an isolated individual. This association of all happenings, as a conception, since it precludes the cutting of information into events or details and a seeming dissociation in what is apparent, should progressively lighten the burden in education. Each bridge, however large, is always in its happenings but a part of another, of all other happenings. A bridge builder aware of this concept does not fool himself while he acts and thinks in terms of events. He, if he be aware of what he is doing, unhesitatingly goes out into the unknown and conceives of a bridge twice as great as has been built according to the formulae to be found in any printed book. With unconscious awareness he portrays in his art what is not apparent to other men. They see only in terms of events as they are adapted in life to their surroundings—as they see with their eyes. Here is the mysterious secret with which Nature plays with complacent man. If his limit in seeing is to be the confines in the happenings in all Nature he must strive to see for himself and to see always beyond where he sees. And Nature through all men goads all men on their way. This appears to be the only way out from the wheel on which individual man feels he is at present whirling faster and faster to his progressive confusion. He constantly takes himself more seriously, an individual so masterful in choosing his deeds! Each man in turn accuses his neighbor and dispenses "justice" and all, even the most antisocial, must live along with their neighbors, with Nature, each and all influencing every one in turn. Yet Nature never counts, measures, repines nor explains, she lives only in the present. She exacts performance and not appraisal, not profession. Only attempted performance leads through a progressive adaptation of each man, by all men, by all nature towards the misty, but attractive, almost limitless possibilities in achievement. Walter Pater has written in "Appreciations": "Experience answers that the dominant tendency of life is to turn ascertained truth into a dead letter, to make us all the phlegmatic servants of routine. The relative spirit, by its constant dwelling on the more fugitive conditions or circumstances of things, breaking through a thousand rough and brutal classifications and giving elasticity to inflexible

principles, begets an intellectual finesse of which the ethical result is a delicate and tender justice in the criticism of human life." Man will continue dissatisfied unless he acquires an unconscious understanding that happiness lies in continuous performance, in the progressive satisfaction of aspiration.

In the continuum, to which all evidence seems to point, no disease, no fracture of bone even, no effort, not even a thought of man has a commencement in an event. In all duration and across all space, in all dimensions, all happenings are of the continuum, of which continuum "each" man and his diseases, his accidents appear to him to be an "event." Is he not a party to the "events" of his great grandfather's milieu as well as to those of his own?

All branches of medicine and surgery require the adventurous explorer, as was John Hunter. Therefore, it is sincerely hoped that the hampering chains of organization will not be too heavily loaded upon thought in medicine and in medical education so that all trends can be more freely followed, even in a surgical laboratory, thus ultimately leading away from an acquiescent attitude of mind and formality in thought to a wider understanding of man, his emotions, his needs, his burdens.

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THE SLOW INTRAVENOUS ADMINISTRATION OF LARGE DOSES OF SODIUM CITRATE.

*A New Method for the Control of Bleeding.**

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When the citrate method of blood transfusion was introduced in 1915, the question that at once arose was whether the intravenous introduction of sodium citrate, recognized as an anticoagulant, would not result in a suspension of coagulation in the recipient's blood. It was soon established conclusively, however, that this did not occur; in fact, a transient shortening of the coagulation time in the recipient, with a subsequent return to the previous level, was found to follow the transfusion of citrated blood. In an effort to seek an explanation for this paradoxical action some experiments were begun by Neuhoof in 1916, and taken up again last year.

The experiments will be reported in some detail at a later date. In brief, they establish the following hitherto undescribed results of sodium citrate injections: 1. The coagulation time is tremendously shortened within a few minutes of the introduction of nontoxic doses of sodium citrate, and this shortened coagulation time is sustained for one or more days. 2. The bleeding time is likewise shortened so that, after citrate injection, large vessels can be

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divided with prompt cessation of hemorrhage. 3. Coincident with the shortened coagulation time the venous blood is altered in color to a light arterial tint. In addition, the experiments demonstrated that there is no fixed toxic or lethal dose of sodium citrate per kilogram of body weight, but that toxicity depends to a remarkable degree upon the rate of introduction of the citrate solution.

Few and incomplete observations have been reported on the effect of sodium citrate administered intravenously in the human being. Weil (1) reported the administration of sodium citrate in one patient, an adult. Five grams of a twenty per cent. solution were injected. The coagulation time was halved; no other data were given. In a case of hemophilia, described by Ottenberg (2), a minute dose (0.6 gram) was followed by a marked drop in coagulation time. Forty-eight hours later a prolongation of coagulation time was found. Kinsella and Brown (3) recently reported an attempt to control the hemorrhagic manifestations in the lungs in influenza by the intravenous introduction of sodium citrate in one gram doses and reported marked effects on coagulation time in five patients. Finally we learned very recently, through the courtesy of Dr. Lewisohn, that Weil attempted to control bleeding in three patients by the intravenous administration of one gram doses of sodium citrate; the results were not published. From none of these reports can one gain any idea of the duration of the changed coagulation time following citrate injections except possibly in Ottenberg's case. In all, with the single exception of Weil's case, very small doses were employed. We have been unable to find any reports in the literature of any study of the possible effects of large doses of sodium citrate on bleeding.

Our clinical observations were begun a year ago and are being continued at the present time. About a hundred injections of large doses of sodium citrate have been given by us, and this report is

Neuhof and Hirshfeld: Sodium Citrate Injections.

based upon the observations made in these cases. The tests used for determining coagulation time will be described elsewhere, and also the evolution of the optimum dose of the drug. We now employ a dose of from six to eight grams for adults and one to three grams for children, and believe that in the former the six gram dose will prove to be the most satisfactory.

Preparation and concentration of the sodium citrate solution.—The solution is prepared by dissolving U. S. P. sodium citrate in distilled water, filtering if necessary. The solution is sterilized in an autoclave. It should not be used unless perfectly clear. We now employ a thirty per cent. solution. The optimum dose being six grams, twenty c.c. of this solution are injected.

Administration.—The solution is usually introduced into a vein at the bend of the elbow through a Fordyce needle with a twenty c.c. syringe. At least ten minutes should be consumed for the injection of the drug. Otherwise it seems to us that serious manifestations may possibly follow, for they were observed in the experiments when citrate solutions were rapidly introduced. Our custom is to inject about two to three c.c., wait a few moments to see if any discomfort is complained of, inject another two to three c.c., and continue in this manner until all the solution is introduced. In the few instances in which we were in doubt as to the advisability of continuing the introduction of the citrate, we preferred stopping at a smaller dose than the one planned. If any of the manifestations to be described appear, we always await their disappearance before the injection.

Since this paper was completed a death following a citrate injection has occurred in another's hands. The solution was not introduced according to our technic. Under the impression that we may possibly not have laid sufficient emphasis upon the slow and intermittent introduction of the solution as

described above, the case is reported in detail. The notes have been obtained through the courtesy of Dr. A. A. Berg and Dr. E. Libman.

CASE.—A woman, sixty-nine years old, was operated upon for common duct stone. Three days after operation there was oozing from the wound, after packings had been removed. As a prophylactic measure against further bleeding a sodium citrate injection was given. Sixteen c. c. of a thirty per cent. solution (4.8 grams) were introduced without pause within a five minute period. Directly thereafter respirations ceased, and the heart stopped beating several minutes later. At the postmortem examination by Dr. E. Libman there was no free blood found in the peritoneal cavity, and no evidence of thrombosis or embolism. There were adhesions from an old pericarditis, marked sclerosis of the thoracic aorta and coronary arteries, and a small carcinoma of the stomach.

It is in a sense fortunate that the first death following a sodium citrate injection should have occurred in a case in which there was a fatal prognosis from the gastric carcinoma, and it is significant that a dose of the drug less than the maximal dose accepted by others should have been followed by death. But the object lesson is clear. We are now no longer in the position of theorizing as to the absolute necessity for the slow and intermittent intravenous administration of sodium citrate, the conclusion derived from our animal experiments. The concrete case establishes the fact once and for all that sodium citrate is a very dangerous drug when injected intravenously without observing the precautions we have taken and advised.

Manifestations after injection of large doses of sodium citrate.—The following have been noted: salty taste, trembling of the lips, tingling sensations in the extremities, dizziness, nausea, a sense of oppression, or tightness across the chest or abdomen. Many patients presented no manifestations referable

Neuhof and Hirshfeld: Sodium Citrate Injections.

to the injection. There have been no untoward aftereffects. No chills or elevation of temperature were observed with a single exception: A patient with a common duct stone and icterus had several chills with fever during his short stay in the hospital and suffered a chill with a rise in temperature one hour after the citrate was given. No alteration in blood pressure had been noted either during or after the introduction of the citrate. Sodium citrate is said to have a toxic effect on the kidneys, but we have been unable to verify this clinically even when very large doses were given. Up to the present the drug has been administered in only one patient suffering from a severe nephritis, and in this instance no toxic manifestations were noted. In short, we wish to emphasize the fact that no evidences of toxicity were observed in any of the hundred injections of large doses of sodium citrate that we have given up to and including a dose of fourteen grams.

Turning now to the effects of large doses of sodium citrate administered intravenously in the human being, we may say at once that they correspond closely to those observed in our animal experiments. A similar drop in coagulation time occurs, the same change of the color of the venous blood to a light arterial tint is usually seen, and in all the cases of bleeding we have been able to observe, the hemorrhage was controlled.

Change in coagulation time.—A typical curve of coagulation time after the optimum dose of six grams may be described as follows, the patient having a coagulation time of ten minutes: Five minutes after the injection the coagulation time drops to seven minutes, ten minutes later it reaches five minutes, in one half hour the coagulation time is between two and three minutes. The peak is reached some forty minutes after the injection, and is sustained in the neighborhood of a two minute coagulation time for an additional hour. The return

Young and Hinchey: Sodium Citrate Injections.

to the normal then begins, but this is much more gradual than the rapid drop after the injection. In six hours the coagulation time reaches five minutes. Twelve hours after the injection it is still about seven minutes. The return to the normal occurs after a variable time; in some instances the normal is reached in twenty-four hours, in others not until forty-eight hours or longer after the administration of the drug. No subsequent changes in coagulation time have been seen in observations taken two, three, four, five and six days after injections. The curve described is typical and figures closely approximating those given have been obtained in every instance in which such frequent observations could be taken. Of noteworthy interest is the fact that the coagulation time was shortened by citrate injections to a similarly striking degree in patients in which it was pathologically prolonged, especially in jaundice. We have noted a drop in coagulation time from sixteen minutes before to two minutes following the injection.

In the past few months almost all patients admitted to our surgical service received citrate injections and the pronounced change in coagulation time was seen in nearly every instance, regardless of the disease from which the patient was suffering. The coagulation reaction following citrate administered in optimum doses did not occur in a very few patients. The condition for which these patients came to the hospital offered no explanation for the absence of the reaction although it is possibly suggestive that three of them were suffering from cirrhosis of the liver with jaundice. The absence of any change in coagulation time following citrate injection in these cases will only be accounted for when the cause of the reaction is clearly understood. The cause of the changes occurring after citrate injection is unknown at the present time.

There are some cases in which a more prolonged effect is desired than that obtained from a single

dose of citrate. We have attempted to sustain the shortened coagulation time by repeating the dose after twenty-four to thirty-six hours. As a result the drop in coagulation time has been maintained in some instances for several days, to return to the normal in about a week; in other cases the second dose has had little or no additional effect. We believe that the subcutaneous or possibly oral or rectal administration of sodium citrate will prove a better method when a slower and more sustained result is desired and we are now engaged in studying this question.

Change in the color of the blood.—The change in the color of the venous blood to an arterial tint is usually present within five minutes of the introduction of the citrate solution. The return to the normal hue of venous blood is noted as the coagulation time again approaches that existing before the injection. In the small group of cases in which the coagulation reaction did not occur no change in the color of the blood was noted and we therefore regard this alteration in color as a characteristic element in the reaction. The appearance is that of venous blood that has been oxidized. We believe that spectroscopic and other studies may demonstrate that oxidization occurs as the result of the citrate injections.

Consistency of the clot.—Concerning the clot that forms in the test tube or at the mouth of an injured vessel, there is every reason to believe that it is at least as solid after citrate injections as normally. In fact, we have gained the impression that a tougher and more solid coagulum results from the introduction of the citrate. The best demonstration of the adequacy of the clot is the permanent cessation of bleeding in the great majority of instances. There was no evidence of intravascular clotting in any of our experiments, and in none of the patients to whom citrate was given was there any suggestion of thrombosis or embolism.

Control of bleeding.—Our evidence of the striking and sometimes remarkable effects of large doses of sodium citrate on bleeding in human beings rests on purely clinical observations. It can truly be said that bleeding would have ceased spontaneously in some or perhaps many of the cases we have studied. Up to the present time, however, bleeding has been checked in every instance in which the citrate injection has been given for that purpose. The best proof that the cessation of hemorrhage is due to the citrate injection is that bleeding regularly begins to be controlled within fifteen minutes after the administration of the drug.

Unless the underlying cause of a hemorrhage is cared for, recurrence of bleeding may of course take place, for the sodium citrate injection is only employed for the immediate control of hemorrhage. For example, a patient suffering from an incomplete abortion had been bleeding continuously for several days; bleeding stopped for twelve hours after the injection, and then recurred and continued until the uterus was emptied. There were three cases in which hemorrhage controlled by sodium citrate recurred after varying periods of time, to be definitely controlled by a second dose of the drug. These were one case of hemorrhage from a colostomy wound for carcinoma of the rectum; one of hemorrhage from the abdominal wall after an exploratory laparotomy for an inoperable carcinoma in a jaundiced patient, and one case of polycythemia with bleeding from the gums after the extraction of several teeth.

In all the remaining cases a single dose of sodium citrate permanently controlled the hemorrhage. These cases may be arranged in four groups:

Internal hemorrhage.—Bleeding was controlled in cases of hematemesis, rupture of the liver, traumatic hemothorax, hemoptysis, and possibly in a case of cerebral hemorrhage.

External hemorrhage.—These cases were varied.

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They included lacerated wounds, hemorrhage from the rectum, bleeding from raw areas left bare by operation, and postoperative hemorrhages from the rectum, gallbladder and prostatic beds.

Bleeding encountered at operation.—There were a number of impressive examples at cranial, abdominal, and other operations. A remarkable instance was a case that proved to be cirrhosis of the liver with icterus. The intravenous injection of citrate was begun as the abdominal incision was made. In exploring the undersurface of the liver an alarming venous hemorrhage was started. Packings absolutely failed to control this, and the bleeding point or area could not be exposed. Without any other measure being employed, the bleeding quite suddenly became less and ceased soon after. The control of the hemorrhage occurred fifteen to twenty minutes after the introduction of the citrate. The excess blood was sponged away and the operation continued without further bleeding.

Bleeding anticipated during or after operation.—In some cases it was difficult or impossible to deduce any effect from the citrate injection because of the necessary sponging at operation. In other instances in which citrate was given the operative field was manifestly less bloody than could have been expected. A striking example was a case of carcinoma in which operation was performed recently by Dr. Lilienthal. A T incision was made, splitting the larynx and widely opening the pharynx transversely to expose the neoplasm. Except for a few arteries that were caught and ligated, the field was entirely free from oozing. Other cases were instances of jaundice with prolonged coagulation time. Examples of anticipated postoperative oozing that did not occur after citrate injection are cases of osteoplastic craniotomy and operations for acute osteomyelitis in which oozing was still going on at the end of operation. In fact, there has not been a single instance of a postoperative hematoma in the wound

since citrate injections have been used as a routine for all cases at the time of operation.

CONCLUSIONS.

1. The slow intravenous administration of large doses of sodium citrate given intermittently over a period of ten to fifteen minutes is nontoxic both experimentally and in the human being. In the latter, massive doses up to fourteen grams have been given without any toxic manifestations.

2. The rapid intravenous administration of sodium citrate is dangerous and may be fatal both experimentally and in the human being.

3. The optimum dose for adults is six to eight grams in a thirty per cent. solution and one to three grams in greater dilution for children. Doses for infants have not been determined.

4. All types of bleeding, internal as well as surgical, that have been encountered, have been controlled by large doses of sodium citrate administered intravenously.

5. Large doses of sodium citrate have been successfully used to obviate hemorrhage in cases in which bleeding was anticipated at operation.

6. This method offers a large sphere of usefulness in the treatment of bleeding, is simple in application, and has proved both nontoxic and safe in our hands.

We wish to extend our thanks to Dr. Howard Lilienthal for his courtesy and hearty cooperation in this work.

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CERTAIN CHEMICAL CHANGES IN THE BLOOD AFTER PYLORIC OBSTRUCTION IN DOGS.

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The operation of closure of the pylorus was performed on eight dogs in an attempt to reproduce the clinical condition known as gastric tetany. Whether or not this, our original, object was attained we are unable to state definitely; in fact, this matter became of secondary interest as soon as we found and became absorbed in the study of the great disturbances in certain fundamental physicochemical equilibria which took place in the blood after this operation.

Tetany is a condition characterized clinically by contractions in the flexor muscles of the extremities and occasionally by generalized convulsive seizures or muscular spasms in other parts. Increased response to galvanic stimulation when applied over the peripheral nerves has been found in about 80 per cent of the cases (Holmes). When this state of nerve hyperirritability is associated with dilatation of the stomach the condition is termed gastric tetany. The gastric dilatation is often consequent to pyloric obstruction, the latter most frequently the result of cicatricial contraction of an ulcer. A common history of such a case would be that of a man who, with a previous story of gastric indigestion, pain, and vomiting, is one day overcome by a more severe attack and after several inordinate fits of vomiting is taken with tetanic convulsions and dies. Autopsy reveals a much dilated atonic stomach with a stenosed pylorus.

A number of theories were advanced in the past to explain the tetany in such cases. None of these, however, was verified by experiment and they simply mirror the fashions and extent of physiological reasoning possessed by the practitioners of the epoch. For instance, there was the mechanical theory that the

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contractions of the stomach against an obstructed pylorus, or in the act of vomiting initiated afferent impulses which sensitized the brain and central nervous system to such a degree that any added stimulus, such as cold or the passage of a stomach tube, would inaugurate convulsions and spasms. More recently other ideas such as those of dehydration and intoxication have been presented, supported only by insufficient experimentation and hasty conclusions.

It has been found that gastroenterostomy would entirely cure the condition (Jonnesco and Grossman) and that the administration of calcium would temporarily alleviate the symptoms (Kinnicutt). These are important findings.

As far as we know, few attempts have been made to produce gastric tetany experimentally. In this laboratory Dr. E. H. Pool performed pyloric closure by various methods on many dogs. The animals developed slight muscular tremors and spasms of various kinds, but only in one case, out of about forty, was he able to demonstrate increased electrical irritability with a cathodal opening current of less than 5 milliamperes. In his judgment, therefore, it was not demonstrated that tetany had been produced by the operations. Little significance was attached to the one exception, as it was considered that this was probably due to some technical error. Because of this experience of one so familiar with the subject of tetany, and because we did not in our experiments make the electrical tests, we cannot claim to have reproduced the condition which is clinically known as gastric tetany.

Seven out of our eight dogs showed muscular twitchings, tremors, spasticity, and fibrillary movements in a room where the temperature was constantly maintained above 70°F. Such manifestations were not seen in dogs undergoing various other gastric or abdominal operations. The eighth dog became paralyzed without showing any increased rigidity as far as could be seen. The electrical tests were omitted, not because we were unaware of their importance in the diagnosis of tetany, but because they would have to have been done to the exclusion of the chemical studies in which we were more particularly interested. MacCallum and coworkers, however, have just published the results of electrical tests performed on dogs with pyloric occlusion which

definitely indicate an increased irritability of the nerves to the galvanic current. In one dog, of the present series, pedal spasms in the fore extremities occurred to such a degree that at times it was almost impossible to straighten his paws. Whether or not these signs were manifestations of tetany we cannot say. The subject is pregnant with possibilities and it is with considerable misgivings that we have had to interrupt our work in its bare inception and present the results of such a short series of tests. However, it is believed that the striking regularity of the figures, to be recorded, not only confirm certain results of other investigators but point to further basic disturbances which offer a field for profitable research in the future.

An interesting study of the effects of pyloric occlusion was that of McCann who recently published a short paper giving figures for the combined CO_2 of the blood. In four dogs he showed that, after closing the pylorus, the alkaline reserve of the blood increased rapidly up to the time of death. Since McCann, as well as Wilson and his coworkers, got similar results after parathyroidectomy, and the latter had showed that injections of hydrochloric acid relieved convulsions, the former thought that tetany in both instances (*i.e.*, after pyloric closure and parathyroidectomy) was the result of a condition of alkalosis. We were unable to verify the results of these investigators after removal of the parathyroids, and so we determined to repeat McCann's gastric experiments. The operative procedure consisted merely in tying a stout string very tightly around the pylorus. The CO_2 -combining capacity of the plasma was determined by the Van Slyke method in the usual fashion. The results are given in Table I.

In Dog M, our first, it was noted at death that the blood was very dark and viscous. Because of this observation we were prompted in the next experiments to make hematocrit readings on each sample of blood. In most cases there seemed to be a tendency towards an increase in the proportion of solid to fluid elements, probably from dehydration, but in those which showed no such changes the symptoms and chemical changes in the blood were equally well marked. In some cases rectal infusions were given to supply fluid. No blood volume estimations were made.

Pyloric Obstruction in Dogs

TABLE I.*

Dog N. Before operation, CO₂ 74.8 vol. per cent; 1st day after operation, 84.5; 2nd day, 93.8; 3rd day, 86.2 and 101.2; 4th day, 98.8; 5th day, 91.7; 6th day, 123.7; 7th day, 117.0; 9th day, 117.0; 14th day, 131.1; killed.

	Dog M.	Dog O.	Dog P.	Dog Q.	Dog R.	Dog S.
	vol. per cent	vol. per cent	vol. per cent	vol. per cent	vol. per cent	vol. per cent
Before operation	66.3	55.6	40.8	52.5	46.7	47.5
1 day after operation	158.0	80.2	62.6	75.8	61.3	60.3
			74.9		63.2	58.3
2 days " "	102.0	77.7	76.8	90.0	70.0	73.9
		83.6		95.7	74.8	96.2
		85.0				
3 " " " "	Death.	Death.	90.0	95.0	73.9	79.7
			Killed.	Killed.	Killed.	Killed.

* Only the figures obtained from samples of blood from the jugular vein have been inserted.

TABLE II.

	Dog M.	Dog N.	Dog R.	Dog S.	Dog O.
	pH	pH	pH	pH	pH
Before operation	7.80	7.82	7.90	7.76	7.74
1 day after operation	7.87	7.88	7.88	7.83	7.75
2 days " " " "	7.87				7.63 (15 min. before death.)
3 " " " " " "	Death.				7.54 (15 min. after death.)

TABLE III.

Calcium per 100 Cc. Serum.

	Before operation.		After operation.	
	mg.		mg.	
Dog M.	10.0		14.0	
Dog O.	9.6 10.3	9.95 (Cells 31.3 per cent.)	12.2 12.5	12.35 (Cells 35 per cent.)
Dog P.	12.3 12.3	12.3 (Cells 39 per cent.)	13.7 (Cells 42 per cent.)	

There seems to be only one conclusion to be drawn from the above results; namely, that partial occlusion of the pylorus is followed by a marked increase in the alkaline reserve of the blood, a condition which has been called alkalosis.

At the same time as these determinations of CO_2 were being made, the pH of the blood was measured by the gas-chain method. The results are given in Table II. The figures seem to show that there is a very slight rise in pH (decrease in H ion concentration) after the operation, but the figures for Dogs M and O show that after this initial rise there is no further increase. There is also the interesting observation that as death approaches, the blood does not become more alkaline as one might suppose if the mechanisms for maintaining the acid-base equilibrium were suddenly overwhelmed by rapidly increasing basic radicals, but on the contrary, just as in death from other causes, there is a rapid premortem fall in pH.

As calcium salt infusions have been found beneficial in gastric tetany, we tested the concentration of this substance in three dogs before and after operation as shown in Table III.

These tests show that the concentration of calcium is not decreased, but on the other hand, is slightly higher than normal. MacCallum using a crude analytical method purely for comparative purposes found no change or an insignificant drop in calcium in these cases. Variable results were obtained for calcium by the analyses of Dr. Greenwald. The latter, who has been perfecting a method for the estimation of certain inorganic constituents of blood, kindly analyzed samples from three of our dogs with results as given in Table IV.

The results of these salt analyses are significant. It is at once apparent that the most definite change is a marked drop in the concentration of chlorides. This pronounced fall (about 50 per cent) was also found by MacCallum, and in fact, it is just what one would expect after pyloric occlusion. The inverse relationship between the concentration of bicarbonate and chloride ions in the plasma has recently been established by McLean and coworkers. Their experiments were concerned with the well known Zuntz phenomenon. In the present series the rise in bicarbonate and fall in chloride concentrations involve the whole blood. Other changes to be noted are (1) the rise in sulfur and

(2) the rise in phosphorus. The concentration of sodium we rather expected to find above normal on account of the tremendous increase of bicarbonate in the blood; in fact, we had turned

TABLE IV.

Plasma		Cells.		Whole blood.			
Before operation.	7 days after operation.	Before operation.	7 days after operation.	Before operation.	2 days after operation.	7 days after operation.	
Dog N.							
	mg.	mg.	mg.	mg.	mg.	mg.	
Cl	411.0	195.0	189.0	103.0	304.0	188.0	151.0
S	13.7	22.7	13.5	17.3	13.6	14.8	20.1
P	5.07	8.52	41.7	54.5	22.8	40.0	30.3
Ca	12.8	13.3	1.01	8.4	7.10	7.62	11.0
Mg	2.65	Lost.	8.05	Lost.	5.26	7.03	Lost.
K	19.4	12.1	29.0	25.3	24.0	25.1	18.4
Na	338.0	265.0	214.0	271.0	278.0	275.0	268.0
Dog Q.							
	Before operation.	2 days after operation.	Before operation.	2 days after operation.	Before operation.	2 days after operation.	
	mg.	mg.	mg.	mg.	mg.	mg.	
Cl	383.0		194.0		304.0	148.0	
S	10.67		10.6		10.7	17.03	
P	6.45		44.6		22.5	43.8	
Ca	15.13	Blood	4.27	Blood	10.6	7.21	
Mg	2.24	clotted.	6.29	clotted.	3.41	6.80	
K	15.6		30.66		21.9	26.1	
Na	351.0		251.0		328.0	265.0	
Dog T.							
Cl	408.0	245.0	212.0	152.0	306.5	185.8	
S	8.61	19.3	9.45	14.2	9.05	15.95	
P	2.34	4.53	54.7	58.9	29.6	39.09	
Ca	10.5	9.83	6.45	6.58	8.4	7.74	
Mg	2.54	3.46	8.47	8.12	5.63	6.41	
K	20.47	19.8	29.5	31.1	25.21	27.0	
Na	343.0	295.0	273.0	254.0	306.7	268.6	

to this expected rise as the most likely explanation for the nervous irritability. MacCallum did not test the sodium but suggested, in his paper, that this be done, intimating, it seems, that the

metal might be found in abnormal amounts. These analyses, however, show that the concentration of sodium is slightly decreased.

In none of our dogs did we see the violent convulsive seizures described by MacCallum. The latter, however, cut across the pylorus, completely closed the lower end of the stomach with sutures, and brought out the proximal end of the duodenum through the abdominal wall. Through this fistula water was regularly injected into the duodenum and periodically the stomach was washed out with a pump. In the present series the pylorus was cut across in only one experiment (Dog T); in the other cases a strong cord was simply tied tightly around the pylorus. At autopsy it was found that the latter procedure had never completely shut off communication with the duodenum, but it was nevertheless sufficient to inaugurate the same chemical disturbances as occurred after complete closure. The animal washed out his own stomach, many times a day, by drinking large quantities of water and then immediately vomiting it up again.

With one exception (Dog O) all our animals had twitches, fibrillations, spasms, and abnormal muscular contractions of various kinds. We feel convinced that these were not the result of such factors as operation, temperature of the room, etc., as there was plenty of opportunity to control such obvious conditions, but rather do we think that they were probably due to the changes in the blood which were invariably found to take place after pyloric occlusion. In Dog O marked paralysis occurred and there were signs of weakness which simulated paresis in two other dogs. This finding is of interest in connection with the work of von Wyss and later that of Grünwald who both believed, as a result of experiment, that paralysis could be produced by decreasing the chloride content of the blood.

A specific function of the chloride ion was also shown to exist when Loeb (1912) discovered that the toxicity of NaBr , Na_2SO_4 , NaNO_3 , etc., for the adult *Fundulus* may be abolished by the addition of NaCl or other chlorides but not by other sodium salts.

RESULTS.

The following changes in the blood were found to occur after closure of the pylorus in dogs:

1. A marked increase in the CO_2 -combining power of the blood.
2. A striking fall in the concentration of Cl ions.

McCann had already demonstrated the rise in alkaline reserve, and, as these experiments were being completed, MacCallum's article was published showing both the increase in bicarbonate and the fall in chloride concentration. In these particulars the tests set down above may be regarded as confirmatory evidence. We differed from MacCallum in that we found:

3. A slight increase in the concentration of calcium in the serum.

It was further shown that:

4. The pH of the plasma, after operation, showed only an insignificant rise; at death it fell rapidly.
5. The concentrations of sulfur and phosphorus were markedly increased.
6. The concentration of sodium was diminished in two out of three cases.

DISCUSSION.

Practically all the dogs in this series developed evidence of hyperirritability. Regardless of whether this was a condition identical with gastric tetany, whether it was another form of tetany, or whether it was not tetany at all, there must be some cause for the phenomenon and one is tempted to provide an explanation on the basis of the blood findings.

The two previous investigators, MacCallum and McCann, who studied the chemical nature of the changes following pyloric occlusion seemed to favor the view that the nervous manifestations were the result of the alkalosis. Particularly did the latter think so, since he also found an increase in the alkaline reserve in parathyroid tetany. Since we believe it has been shown that there is no increase in the bicarbonate content of the blood after parathyroidectomy and as there are no fundamental studies to our knowledge which indicate that an alkalosis, as such, can produce hyperirritability of nerves, we believe that it cannot be

fairly maintained that this is the cause. However, we have no conclusive proof that this theory is untenable nor have we any other satisfactory explanation to offer. Possibly it is concerned with the equilibrium of certain electrolytes in the body, particularly the disturbance of the ratio between monovalent and divalent anions and cations. The work of Loeb, Mathews, Lillie, and others on the antagonism of ions is very suggestive. Their experiments tend to show that an increase in the relative proportion of monovalent cations and divalent anions will augment the normal irritability of nerve tissue; a condition which may be counteracted by the addition of a salt such as CaCl_2 having a divalent cation linked with a monovalent anion. The most marked changes in the present series involve an increase in carbonate and phosphate ions (divalent) and a diminution of chloride ions (monovalent) which according to the theory should bring about hyperirritability. The slight increase in calcium and decrease in sodium in the blood may represent an adaptation on the part of the body to the above mentioned disturbance in the *milieu interieur*.

The explanation for the blood changes observed seems fairly clear. The alkalosis is evidently an exaggeration in duration and extent of the alkaline tide occurring normally after meals. The formation and secretion of HCl by the cells of the gastric mucosa necessitate the removal from the blood stream of H ions and Cl ions. The former exist in the blood mostly as carbonic acid, the latter in the form of sodium chloride. This process of selective secretion liberates bicarbonate ions and sodium ions which unite to form sodium bicarbonate and, in this fashion, bring about an increase in the alkaline reserve.

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OBSERVATIONS ON PARATHYROIDECTOMIZED DOGS.*

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Recent researches have resulted in the formulation of three independent, but not necessarily contradictory, theories concerning the blood changes that follow parathyroidectomy, and the relationship of these changes to the symptoms.

The first of these holds that the symptoms following the removal of the parathyroids are due to a disturbance of salt metabolism, particularly that of calcium. This hypothesis is based essentially upon the fundamental studies of Loeb (1902, *a*) and of J. B. MacCallum relating to the effect of various ions on nerve excitability, upon the suggestive experiments of Sabbatani on the opposing effects of applying calcium chloride solutions and calcium-precipitating solutions to the cerebral cortex, and finally upon

* The present research had its origin in some tests made on four dogs whose parathyroids had been removed as part of the regular course of surgical instruction given to the third year class at the College of Physicians and Surgeons. The results of these early experiments were not entirely in accord with generally accepted opinion, and so we were impelled to repeat them in a more systematic manner with the addition of a few other tests which seemed to be of importance. After eleven thyreoparathyroidectomized dogs had been studied, force of circumstances brought about the termination of the investigation. It has been repeatedly shown, and it seems to be almost universally accepted, that the immediate effects of thyreoparathyroidectomy are similar to those of parathyroidectomy. As parathyroid tissue is not infrequently imbedded within the body of the thyroid gland, by removing the latter the chances of complete parathyroidectomy are enhanced. If the number of experiments in this series is considered meager it is hoped that this deficiency will be somewhat compensated for by the consistency of the results.

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Quest's quantitative analyses of the brain for calcium after tetany. Parhon and Ureche were the first to note the curative effect of calcium salts in tetany and quite independently MacCallum and Voegtlin found in 1908 that the calcium concentration in the blood and tissues was decreased and in the feces and urine was increased after parathyroidectomy. Other chemical investigations soon followed among which may be mentioned the researches of Greenwald (1911) which indicated that the phosphates were increased in the blood and urine during tetany.

The second theory introduced by Wilson, Stearns, and Thurlow placed emphasis on a disturbance of the acid-base equilibrium. These investigators gave evidence to support the view that up to the onset of tetany there was a gradual increase in the alkaline reserve of the blood. During the convulsive seizures enough acid was formed, they thought, to neutralize the excess base and in some cases even to produce a condition of acidosis. The beneficial effects of injections of hydrochloric acid upon the tetany seemed to confirm their theory (Wilson, Stearns, and Janney).

Finally, there may be mentioned a third or toxic theory brought forward in 1915 by the British physiologists, Paton, Findlay, and Burns, which called attention to a highly toxic tetany-producing substance of protein origin found in the blood and urine following parathyroidectomy. This hypothesis seems to have been suggested by the work of Pekelharing and van Hoogenhuyze on the relation of the creatine of muscle to its tonicity, and by the finding of methyl guanidine, a product of protein metabolism, in relatively large amounts in the urine of parathyroidectomized dogs by Koch. Paton and his collaborators showed that injections of guanidine and methyl guanidine would produce a condition of hyperirritability associated with convulsions very much like parathyroid tetany.

Other important experiments, principally along the three lines outlined above, have been performed in various laboratories, but their review would scarcely be relevant to the subject matter of this article. For bibliographies the reader is referred to the theses of Paton and Findlay, Howland and Marriott (1917-18), Ochsner and Thompson, and for a very interesting general discussion of the present status of the subject to a recent article by Voegtlin.

The present research has been limited to an investigation of (1) the blood serum calcium, (2) the alkaline reserve of the blood plasma, (3) the hydrogen ion concentration of the blood plasma, (4) the blood sugar, and (5) the symptomatology.

1. Calcium.

MacCallum and Voegtlin found that the blood of dogs killed during parathyroid tetany contained on an average about 5.4 mg. of calcium per 100 cc. of whole blood; whereas, normally there were found about 13.3 mg. 4 years later, MacCallum and Vogel using a different analytical method found an average of 2.7 mg. of calcium per 100 gm. of whole blood in tetany as against 6.1 mg. in normal dogs.¹ Numerous other experiments were done later by MacCallum and his coworkers, all of which helped to substantiate their original hypothesis that the tetany was the result of calcium deficiency (MacCallum, Lambert, and Vogel, MacCallum and Vogel). Among other things it was found that the injection of calcium salts was the most efficacious temporary remedy for the tetanic convulsions. Some of this work has been brilliantly confirmed in a recent article by Howland and Marriott (1917-18) on infantile tetany, but contested, on less conclusive evidence to be sure, by Cooke, Musser and Goodman, Leopold and von Reuss, Stoeltzner, and others who report contradictory or negative calcium findings. In view, then, of this disagreement, and because no estimations to our knowledge had been made of the calcium content of the blood at various stages after parathyroidectomy, the following tests were undertaken.

The method devised by Halverson and Bergeim for the quantitative estimation of calcium in blood serum was used throughout. Although in our hands it was subject to an error of ± 5 per cent, it was found satisfactory for the purpose. It should be noted that, as there is little calcium in the corpuscles (Cowie and Calhoun), the concentration of this substance in 100 cc. of whole blood is only about two-thirds of the quantity in 100 cc. of serum. The calcium concentrations at various stages after parathyroidectomy are shown by the results given in Table I and Fig. 1.

¹ Normal figures for whole blood obtained recently by more accurate methods would indicate that these latter figures were more nearly correct.

TABLE I.

	Ca per 100 cc. serum.
Dog A.	
Before operation.....	11.5
10 days after operation and 8 hrs. after first and only attack of mild tetany.....	8.2
18 days after operation, apparent recovery.....	10.8
Dog B.	
Before operation.....	11.2
10 days after operation, no tetany. Complete recovery.... (All parathyroid tissue was probably not removed in this dog.)	11.1
Dog C.	
Before operation.....	10.4
4 days after operation, at onset of third attack of tetany...	6.2
10 " " " and $\frac{1}{2}$ hr. before death.....	4.3
Dog E.	
Before operation.....	11.7
21 $\frac{1}{2}$ hrs. after operation, apparently well.....	8.0
5 days " " immediately before first attack of mild tetany.....	4.6
20 days after operation, very weak, continuous fibrillary twitchings.....	4.9
Dog F.	
Before operation.....	10.6
26 hrs. after operation, restless.....	9.0
33 $\frac{1}{2}$ " " " early mild tetany.....	6.7
47 $\frac{1}{2}$ " " " at height of first attack of acute tetany.....	7.0
3 days after operation, 3 hrs. after start of second attack of acute tetany.....	5.1
Dog H.	
Before operation.....	12.0
5 hrs. after operation.....	9.5
20 " " " slight rigidity.....	8.1
39 " " " at onset of first attack of acute tetany.....	6.2
3 days " " slight spasticity.....	5.3
8 " " " spastic, very weak, and cachectic.....	5.0

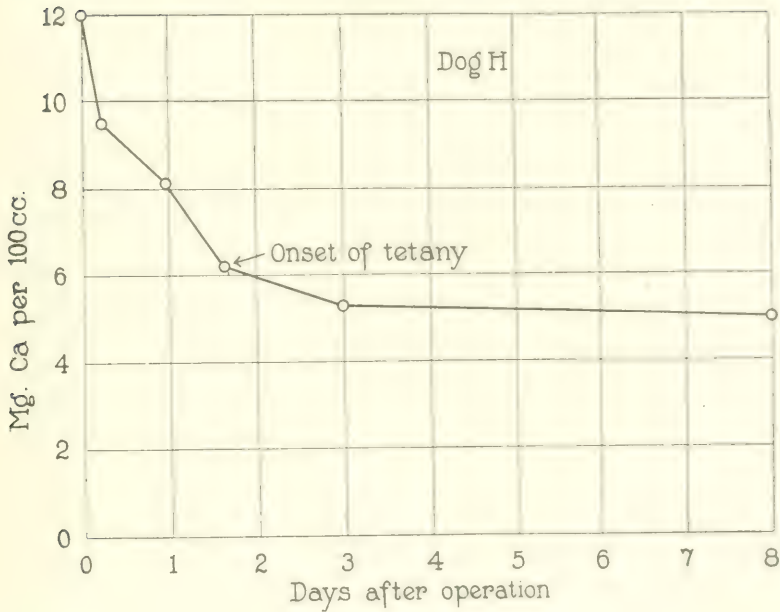


FIG. 1.

The effect of the injection of calcium chloride on the concentration of calcium in the blood is shown by the following figures:

Dog F.

	Mg. Ca per 100 cc. of blood.
During acute tetany.....	5.1
Injection of 40 cc. of 1 per cent CaCl_2 solution; followed by complete relaxation and cessation of convulsions 30 min. later.....	9.0

These tests show that the concentration of calcium in the blood commences to decrease rapidly soon after the removal of the parathyroids, and in a few days reaches a value which is about 40 per cent of the normal. From then on until death there is little, if any, drop. These findings are consistent with the values in infantile tetany and in two parathyroidectomized dogs as found by Howland and Marriott (1916), and in a case of adult tetany recently reported (Barach and Murray). The injection of 40 cc.

of 1 per cent calcium chloride raised the amount in the blood to normal. This temporary curative power of intravenous CaCl_2 injections for tetany we were able to demonstrate repeatedly.

TABLE II.

	100 gm. plaster.			100 gm. cells.		
	Before.	After.	Change.	Before.	After.	Change.
Dog E. Before, and 20 days after, thyreoparathyroidectomy.						
	mg.	mg.	per cent	mg.	mg.	per cent
Chlorine...	284.0(?)	336.0	Uncertain.	197.0(?)	184.0	Uncertain.
Sulfur.....	6.33	8.85	40+	10.7	12.1	13+
Phosphorus	5.08	7.05	38+	45.7	49.0	8+
Calcium	9.14	4.91	46-	3.19	1.87	41-
Magnesium.	2.09	Lost.		5.81	Lost.	
Potassium..	20.2	"		29.6	"	
Sodium.....	344.0	"		214.0	"	
Dog J. Before, and 6 days after, thyreoparathyroidectomy.						
	mg.	mg.	per cent	mg.	mg.	per cent
Chlorine	385.0	378.0	None.	245.0	218.0	10-
Sulfur.....	9.60	11.1	16+	9.31	12.7	36+
Phosphorus	5.03	5.95	18+	46.9	47.3	None.
Calcium...	13.1	8.41	36-	2.32	6.47	180+
Magnesium.	Lost.	2.07		Lost.	Lost.	
Potassium..	"	14.63		"	30.7	
Sodium.....	"	319.0		"	258.0	
Dog K. Before, and 2 days after, thyreoparathyroidectomy.						
	mg.	mg.	per cent	mg.	mg.	per cent
Chlorine...	401.0	412.0	None.	211.0	244.0	15+
Sulfur.....	9.52	10.3	8+	9.09	10.7	17+
Phosphorus	2.71	4.19	55+	51.9	50.8	None.
Calcium	11.6	7.85	41-	6.98	8.2	17+
Magnesium.	1.83	1.84	None.	6.08	5.53	9-
Potassium..	22.3	17.2	23-	32.9	35.8	10+
Sodium.....	322.0	319.0	None.	251.0	289.0	15±

Dr. Greenwald, who was in the process of perfecting a method for the estimation of the principal inorganic constituents of blood, very kindly consented to do some determinations for us. His results are presented in Table II.

Unfortunately these statistics are not complete. The figures corroborate our serum calcium findings and show an increase in

sulfur and phosphorus. Greenwald himself in a former paper (1911) has already drawn attention to the rise in the phosphates of the blood after parathyroidectomy. The high sulfate concentration is in harmony with the observation of Marine that feeding large amounts of sulfur favors the development of tetany. The other figures are too meager to furnish material for deduction.

2. The Alkaline Reserve of the Blood Plasma.

Morel was probably the first investigator to state that a condition of acidosis followed parathyroidectomy, and to affirm that this was the essential cause of the ensuing pathological phenomena. He based his opinion mostly on the high concentration of ammonia and lactic acid in the blood.

Quite an opposite view was presented in 1915 by Wilson, Stearns, and Thurlow, who reported some interesting experiments performed upon parathyroidectomized dogs in the Hunterian Laboratory of the Johns Hopkins University. Determinations of Barcroft's dissociation constant of oxyhemoglobin in venous blood brought into equilibrium with a constant tension of carbon dioxide and measurements of the carbon dioxide tension in the alveolar air seemed to show an increasing alkaline reserve (so called alkalosis) up to the onset of tetany. This was based on the work of Barcroft, who found that the dissociation of oxyhemoglobin varied with the H ion concentration in samples of normal blood, but he did not show, and it does not necessarily follow, that the same relationship will hold for pathological blood, especially in a condition which has been shown to be associated with a disturbance in the equilibrium of electrolytes. The vitality of the alkalosis theory, however, was strengthened in 1918 when McCann published figures for the combined CO_2 after parathyroidectomy. To be sure, this investigator only removed the parathyroids in two dogs, one of which was subjected to gastric lavage—a procedure which may affect the CO_2 tension in the blood—but, as his results showed such a decided rise in alkaline reserve after operation, we were entirely prepared to obtain much the same values.

In the determinations which are about to be recorded, the blood was usually collected from the external jugular vein into a centrifuge tube containing oxalate crystals, and immediately tested

according to the technique of Van Slyke and Cullen. In a number of instances, however, blood was taken from the external saphenous vein, and these samples gave appreciably lower figures than the specimens obtained from the jugular vein. In one series, in which the blood was collected under oil, the results seemed to be a trifle higher than usual; but as no particular advantage seemed to be associated with this extra precaution it was discontinued.

In the following incomplete preliminary tests blood was taken from the saphenous vein:

Dog A.

	Plasma CO ₂ capacity, vol. per cent
1 day after operation.....	33.8
2 days " " and 9 days before onset of tetany....	40.4

Dog C.

1 day after operation.....	46.6
2 days " "	40.4
3 " " "	39.5

In the next two experiments (Table III) blood was collected under oil from the jugular veins unless otherwise stated.

In the experiments given in Table IV, the blood was collected into an open tube from the jugular vein.

The determinations given in Tables III and IV and Fig. 2 indicate that after parathyroidectomy the CO₂-combining capacity of the blood is slightly diminished. This drop is only appreciable, however, for a short period after the operation (the usual postoperative acidosis) and to a lesser degree at the onset of acute tetany. With the exception of a single value noted above, the figures do not present the slightest evidence of an alkalosis; in fact, they represent relatively normal values for venous blood, the collection of which was made at different times with respect to meals and attended at times by more or less struggling on the part of the animal.

An unusual observation was made in Dog E. It was found that after running on the treadmill for an hour or more the combining capacity of the plasma for CO₂ and the CO₂ content were greater than before. This is contrary to the findings in Hastings'

55 experiments with normal dogs in which a decrease in CO_2 capacity was invariably found after exercise. Moreover, in normal dogs no significant changes in the H ion concentration have been

TABLE III.

	Plasma CO_2	
	Content.	Capacity.
Dog E.		
Before operation	66.7	73.3
1 day after operation, apparently well	61.5	76.7
2 days " " restless	69.5	69.6
3 " " " no change	52.5	61.1
4 " " " seems quite normal (after which dog was run on treadmill for 1 hr.)	52.2	64.3
5 days after operation, early signs of tetany	54.8	64.3
7 " " " apparently recovered		72.9
14 " " " thin, but apparently well (after which dog was run on treadmill for 2 hrs.)		73.9
19 days after operation, very cachectic and sick	57.7	61.3
31 " " " very much emaciated, limbs spastic.		
12.15 p.m.		65.3
Gasping respirations, 12.45 p.m.		51.7
9.30 p.m.		65.3
32 days after operation, found dead, 7.30 a.m.		
Dog F.		
Before operation		51.0*
1 day after operation, 4 hrs. before onset of mild tetany		51.0*
2 days after operation, at onset of violent convulsions		38.5*
3 days after operation, quiet	50.5	51.5
4 " " " mild tetany	51.6	51.5
6 " " " fibrillary twitchings	56.7	47.8
7 " " " very sick	61.7	79.7†
8 " " " extreme cachexia	62.9	62.4
9 " " " found dead		

* Blood from saphenous vein.

† No explanation for this wide variation is available.

TABLE IV.

			Plasma CO ₂ capacity.
Dog H.			
			<i>vol. per cent</i>
2 days before operation			68.1
1 day	"		64.3
5 hrs. after	"	good recovery	51.3
15 "	"	slight rigidity	54.8
26 "	"	seems well	58.6
39 "	"	onset of acute tetany	49.0
3 days	"	resting quietly	54.8
8 "	"	very sick and spastic	43.8
Dog J.			
4 days before operation			52.8
1 day	"		57.9
3 hrs. after	"	excellent recovery	48.5
21 "	"	nervous and restless	51.9
27 "	"	restless	53.8
2 days	"	twitches and tremors	49.4
3 "	"	4 hrs. before attack of acute tetany	51.9

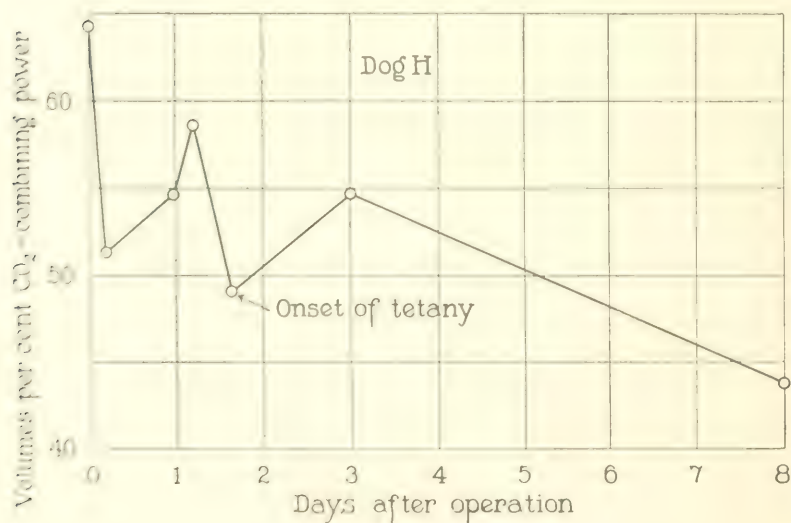


FIG. 2.

detected after exertion, whereas in this animal a marked fall in pH was noted.

Dog E.	CO ₂ capacity.	CO ₂ content.	pH
	vol. per cent	vol. per cent	
Nov. 25, 1919. Before exercise.....	64.3	52.2	7.61
After ".....	70.0	74.2	7.52
(Exercise consisted in running on the treadmill for 1 hr.; distance 4.76 miles.)			
Dec. 5. Before exercise.....	73.9		
After ".....	76.8		
(Exercise lasted 2 hrs.; distance 10.2 miles.)			

The increase in the content of plasma carbon dioxide and the definite fall in pH after exercise would point, it seems, to some disturbance in the mechanism for eliminating CO₂, but how this might have been brought about in this instance is not clear.

3. *The H Ion Concentration of the Plasma.*

Wilson estimated the alkalinity of the blood in a few parathyroidectomized dogs by the method of Levy, Rowntree, and Marriott both before and after shaking out the excess of CO₂. No variations in pH were found in blood samples tested immediately after collection, but in those which were shaken, small increases were noticed. This, however, simply confirmed the original high values for the alkaline reserve found by other methods and did not give indications of variations in the pH of the blood in the body. Recent demonstration of the fundamental mechanisms involved in maintaining the acid-base equilibrium had taught us not to look for any appreciable change in the H ion concentration of blood except, possibly, just before death (Henderson). With the idea, however, that there might be slight variations during life and greater changes just before the death of the parathyroidectomized animal, H ion determinations were made by the gas-chain method.

Aside from the following modifications, the technique of these determinations was that employed in most exact H ion measurements made by means of the potentiometer. A Clark hydrogen

TABLE V.

	Reaction.	Temperature.
Dog E.		
	<i>pH</i>	<i>°C.</i>
Before operation.....	7.64	15
1 day after operation, good recovery.....	7.80	16
2 days " " very lively.....	7.80	16
3 " " " restless.....	7.70	16
4 " " " apparently well.....	7.61	17
(After removing the blood, dog was run for 1 hr. on treadmill.)		
5 days after operation, onset of mild tetany....	7.68	20
10 " " " emaciated.....	7.80	13
31 " " " cachexia, spastic, 12.15 p.m.....	7.73	14
Gasping respirations, 12.45 p.m.....	7.45	14
9.30 p.m.....	7.56	11
32 days after operation, found dead, 7.30 a.m....		
Dog F.		
Before operation.....	None taken.	
3 days after operation, 6 hrs. after attack of acute tetany had been cured by CaCl_2 injection....	7.70	16
4 days after operation, mild tetany.....	7.76	15
6 " " " fibrillary twitchings....	7.59	16
7 " " " apathy.....	7.57	17
8 " " " extreme cachexia, 12.00 m.....	7.65	17
Found dead, 9.00 a.m....		
Dog H.		
Before operation.....	7.77	12
8 days after operation, spastic but no real convulsions.....	7.77	13
Dog K.		
Before operation, 9.45 a.m.....	7.60	20
Operation, little bleeding, 2.30-3.00 p.m.....		
After operation, good recovery, 4.55 p.m.....	7.63	20
1 day after operation, twitching, 9.15 a.m.....	7.61	20
Restless, 2.30 p.m.....	7.63	20
2 days after operation, spasmodic twitches, 6.00 a.m.....	7.63	17

TABLE V—*Concluded.*

	Reaction.	Temperature.
Dog L.		
Before operation, 9.50 a.m.	pH 7.70	°C. 20
Operation, moderate hemorrhage, 3.10–4.00 p.m.		
After operation, good recovery, 5.00 p.m.	7.63	20
1 day after operation, shivering, 9.20 a.m.	7.63	20
Twitches, 2.35 p.m.	7.64	20
2 days after operation, mild tetany, 6.10 a.m. ...	7.65	17
Onset of acute tetany, 12.45 p.m.	7.64	18

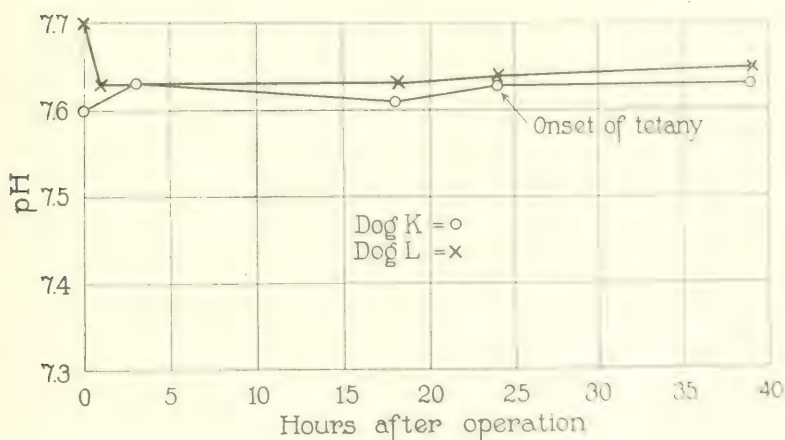


FIG. 3.

electrode was so adapted that the blood plasma, collected, separated, and kept under oil, could be admitted to the gas chamber without exposure to the air. After equilibrium had been reached by shaking, the plasma was replaced by a new sample, and this procedure repeated until no change in the H ion concentration, due to loss of CO_2 , occurred. The temperatures at which the H ion determinations were made are given in the last column of Table V. Because of the present disagreement between investigators regarding the magnitude of the change in pH determinations made at 18° and 38° , we have not attempted to report our

values at body temperature. With the provisional acceptance of Michaelis' temperature correction of 0.21, however, it is seen that the average of all our pH determinations is 7.45, a value very close to that regarded as the reaction of normal blood.

It is to be noted that, just as in our estimations of calcium, CO_2 , and sugar, the later experiments (*i.e.* in this case Dogs K and L) gave the most uniform results (Fig. 3). We are of the opinion that the increased constancy was mostly due to better technique and, therefore, the latter figures are probably more accurate. If this is true we may infer that the H ion concentration of the blood remains relatively constant after parathyroidectomy.

4. Blood Sugar.

Underhill and Blatherwick have found that blood sugar was low after parathyroidectomy. Their determinations made with the method of Forschbach and Severin showed extraordinary varia-

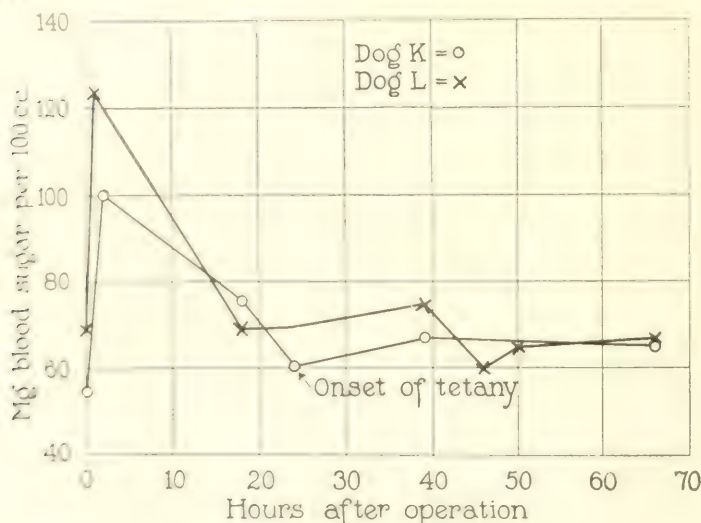


FIG. 4.

tions and were not accompanied by sufficient data to allow for much comment. Watanabe's figures before and after the injection of the tetany-producing methyl guanidine were more uniform,

		Glucose per 100 cc. blood.
Dog E.		
		gm.
Before operation, 9.00 a.m.		0.074
1 day after operation, well, 9.00 a.m.		0.095
2 days	" " restful, 8.00 a.m.	0.070
3	" " no symptoms, 8.00 a.m.	0.071
4	" " " " 9.00 "	0.096
5	" " " onset of mild tetany, 8.00 a.m.	0.079
7	" " " no symptoms	0.087
19	" " " marked emaciation, sick	0.111
31	" " " very sick, last stages, 12.15 p.m.	0.109
	Gasping respirations, 12.45 p.m.	0.121
32 days after operation, death.		
Dog F.		
3 days after operation, and 5 hrs. after cessation of acute tetany following CaCl_2 administration, 9.00 a.m.		0.135*
4 days after operation, mild chronic tetany, 4.00 a.m.		0.079
6	" " " fibrillary twitchings, 9.00 a.m.	0.083
Dog K.		
Before operation, 9.45 a.m.		0.054
2 hours after operation, 4.55 p.m.		0.100
1 day	" " twitches, 9.15 a.m.	0.075
	Restless, 2.35 p.m.	0.060
2 days after operation, twitches, 6.00 a.m.		0.067
3	" " " very lively, 9.30 a.m.	0.065
Dog L.		
Before operation, 9.50 a.m.		0.069
1 hr. after operation, 5.00 p.m.		0.123
1 day	" " shivering, 9.20 a.m.	0.069
	Twitches, 2.35 p.m.	0.069
2 days after operation, mild tetany, 6.10 a.m.		0.075
	Onset of acute tetany, 12.45 p.m.	0.060
	Acute tetany, 2.15 p.m.	0.065
3 days after operation, mild	" 9.40 a.m.	0.067

* This high value may be a sequela of the convulsion, or the result of the calcium injection.

however, and likewise showed a fall. Our few estimations done by the MacLean method,² however, do not confirm their results.³

The tests recorded in Table VI and Fig. 4 show that, in our series, at least, there was no marked disturbance in sugar metabolism for the first few days after operation. The previously observed postoperative hyperglycemia seems to be the only variation from the normal.

5. *Symptomatology.*

The phenomena following removal of the parathyroid bodies in dogs have been described many times in the past, and in these experiments there were abundant opportunities to witness and verify the train of events as usually recorded. We could not find in the literature any but the most incomplete and casual mention of certain other less obvious symptoms which may have some bearing on the final solution of the problem and, therefore, will be briefly discussed at this point. In the first series of experiments a number of striking signs were noted which pointed to a widespread stimulation of the parasympathetic nervous system and immediately suggested an explanation for the much discussed but exceedingly obscure function of the parathyroids. These symptoms were as follows: epiphora, followed by purulent conjunctivitis, enophthalmos with narrowed eye-slit, increased watery nasal secretion leading to rhinitis, increased salivation with foaming at the mouth just before tetanic attack, increased labored respirations with expiratory wheeze, respiratory pulse, irregular heart rate characterized (in the last stages) by dropped beats and sinus arrhythmia, vomiting, diarrhea, frequency of urination and pollakiuria, sexual excitement, and increased coagulation time of the blood. Some of these manifestations have been proved experimentally, whereas others have been supposed on clinical grounds to be of parasympathetic origin. The very characteristic tachypnea, however, did not seem to be the result of a constriction of the bronchial musculature since neither large doses of adrenalin nor atropine had an alleviating effect. The phenomenon might,

² The average of about 100 normal determinations of dog blood done by the MacLean technique in this laboratory is 0.069 gm. per 100 cc.

³ We are indebted to Mr. T. H. Ford for most of the determinations of blood sugar reported in this paper.

however, be the result of increased irritability of the respiratory center. The coagulation tests were made in a small glass tube into which blood was admitted from the bottom through a pet-cock attached to a Luer needle. Blood was collected from the external saphenous vein. The technique has recently been described by King and Murray. The summary of the results is given in Table VII.

Taken as a whole these symptoms represent a rather clear picture of vagotonia, as described by Eppinger and Hess. In the later experiments after more careful observation it became evident that the parasympathetic system was not exclusively affected.

TABLE VII.

	Before operation.		After operation.
	<i>min.</i>		
Dog A.	11	2 days after operation, 8 days before tetany.	14
Dog B.*	18	No tetany.....	16
Dog C.	9	2 days after operation, 3 hrs. before tetany	12
Dog D.	10	1 day " " 1 day " "	12
Dog E.	10	20 days " " chronic tetany.....	15
Dog H.	11	8 " " " " " "	16

* There was no apparent cause for the high figures obtained in this dog.

The evidence of sympathetic excitability was given by the following: dilation of the pupil, the projection of the nictitating membrane across the eyeball, tachycardia, and fever. The following symptoms may be included in this review although their interpretation on the basis of the autonomic system is questionable: sneezing, hiccough, loss of appetite, Cheynes-Stokes respirations, itching of the skin, and weakness. Falta and Kahn, Halsted, and others have recorded some of these signs but little significance has been attributed to them. It is of more than passing interest to note in connection with the conjunctivitis of these dogs with low blood calcium the finding of Chiari and Januschke that calcium chloride injections would prevent the inflammation of the eyes produced by oil of mustard.

We believe that the most likely explanation of these abnormal physiological events is that there exists after parathyroidectomy

an increased autonomic excitability which parallels similar changes in the voluntary nervous system and that this state involves both the parasympathetic and sympathetic divisions, but more particularly the former. This conclusion agrees, in the main, with that of Faltz and Kahn and Hoskins and Wheelon.

RESULTS.

After thyreoparathyroidectomy in a series of dogs, the findings were as follows:

1. The pH of the plasma remained within normal limits.
2. The carbon dioxide-combining capacity of the blood was slightly diminished. This fall was appreciable, however, for only a brief period immediately after operation, and during the hyperpnea at the onset of tetany. No other changes were regularly noted in the alkaline reserve.
3. The calcium content of the serum decreased in a few days from a normal value of about 11 mg. per 100 cc. to about 5 mg., a concentration which was hardly diminished subsequently. When the serum calcium reached a concentration of approximately 7 mg. tetany developed.
4. Two analyses by Greenwald showed that phosphorus and sulfur were increased in the blood.
5. Sugar analyses demonstrated the previously recorded post-operative hyperglycemia, but showed no other significant changes in glucose metabolism during the first few days following operation.
6. Certain of the less obvious symptoms were noted. They seemed to be manifestations of an increased irritability of both the sympathetic and parasympathetic systems.

Since these experiments were finished, there have appeared in the literature two papers confirming the above results for the CO₂-combining power of the blood; a short series of tests included in an article by MacCallum and his coworkers (1920) on gastric tetany, and a more complete series of Van Slyke CO₂ determinations made by Togawa. The latter got slightly lower figures than ours, and believed they were sufficiently abnormal to entitle the condition to consideration as an acidosis. In looking over the more difficultly obtainable literature, we also found that another investigator (Segale) had measured the pH of serum after parathyroidectomy and had likewise found it unaltered. We have discovered no confirmation for our sugar values.

DISCUSSION.

The results of our experiments have not led us to any clear conclusion as to the function of the parathyroid glands or the fundamental disturbances which follow their removal. The decrease in the calcium content of the blood is one very definite and important change which occurs, the significance of which rests upon the fundamental work of Loeb and others who showed that the maintenance of the normal irritability of muscle and nerve is dependent upon an undisturbed equilibrium between various electrolytes in the surrounding medium, and that certain divalent cations were antagonistic to monovalent cations in their influence upon nerve excitability. More specifically, it was found that nerves bathed in a solution of NaCl became, after a certain latent period, chemically stimulated. If, however, a definite concentration of CaCl_2 was added to the solution, no such effect was obtained. Loeb (1899-1900) regarded the Na and Ca ions as antagonistic and the solution which contained them both in proper proportions as a physiologically balanced solution. Fühner, attracted by Loeb's work, suggested in 1908 the possibility of an increase in the ratio $\frac{\text{monovalent ions}}{\text{divalent ions}}$ as the cause of tetany. Later Loeb and Ewald considered the chemical stimulation of nerves in more detail, stressed the greater importance of the cations as compared with the anions, and discussed the possible relationships between stimulation and rate of diffusion. Loeb (1915) found that to preserve normal irritability, the ratio of $\frac{[\text{Na}] + [\text{K}]}{[\text{Ca}] + [\text{Mg}]}$ must be maintained fairly constant and the amount of Ca required to neutralize Na would vary in direct proportion to the concentration of the latter. That the cations are not alone concerned has been shown by Mathews, Lillie, Loeb, and others. Mathews listed a number of sodium salts according to their power to stimulate nerves; as the cation was the same in each case the differences observed were apparently due to the anions. The list was very similar to one made by Loeb a few years before. Finally, Raber has recently reported the results of researches on the effect of anions on the conductivity of living protoplasm. All these experiments seem to show the same thing; namely, that

anions have a definite effect (although to a less degree than the cations) on the chemical stimulation of nerves. The monovalent anions tend to act in the same fashion as the divalent cations, *i.e.* they have an inhibiting effect; whereas the salts with divalent anions are relatively more irritating. If these results may be applied to human problems one would expect to find that the injection of a salt with monovalent cations and divalent anions would provide a maximal irritating effect, whereas a salt with a divalent cation and monovalent anion would be inhibitive.

In 1898 Münzer produced tetany by injecting various sodium salts. According to the theory, any sodium salt, if injected in sufficient quantity, should increase nerve irritability, because cations are more important than anions, and adding sodium $\frac{\text{monovalent cations}}{\text{divalent cations}}$ would, of course, serve to increase the ratio.

He found that sodium bicarbonate and sodium phosphate brought on convulsions sooner than sodium chloride, which also agrees with the theory since the injection of the former would tend to increase the ratio $\frac{\text{divalent anions}}{\text{monovalent anions}}$. Binger induced convulsions in dogs by injecting sodium phosphate solutions of various H ion concentrations. He found that tetany was more readily obtained with Na_2HPO_4 than with NaH_2PO_4 solutions. He attributed the potency of these mixtures to the phosphate ion, which was doubtless in some measure correct. But the sodium ion is probably the more important of the two and the greater toxicity of the disodium mixture would be explained on this basis. A case of transient tetany recently occurred at the Presbyterian Hospital, New York, after sodium bicarbonate administration, another case was reported by Harrop from the wards of the Johns Hopkins Hospital, and other similar instances have been recorded elsewhere. There is a case on record of tetanoid seizures following a rectal infusion of large amounts of saline (Campbell).

All available data, however, do not agree with the theory. Greenwald, for instance, found that in his hands tetany was produced with more facility by sodium chloride than by sodium phosphate solutions. However, other complicating factors such as osmotic phenomena and the rate of excretion of the various

ions by the kidney might account for some of the apparently discordant results. In the light of our carbon dioxide determinations it is hard to understand the beneficial results obtained by Wilson and coworkers when HCl was injected intravenously. It may be that the explanation lies in the fact that such an injection besides adding monovalent anions greatly alters the ratio between other important ions in the blood, the maintenance of which seems to be important. Much conflicting evidence has been presented in regard to various therapeutic measures in tetany which it is difficult to explain. The attacks of tetany following parathyroidectomy vary both in severity and extent. It is difficult to pass judgment on the many temporary cures for the tetanic seizures which have been reported, as the attacks are usually self-limited, often ending abruptly without treatment. After a few days, the animal lapses into a torpor which is not characterized, as a rule, by typical convulsions, but rather by a continuous spasticity with intermittent twitchings and fibrillary movements of such mildness in comparison to the terrible seizures of the previous period that the unwary may easily ascribe the apparent improvement to medication. The dogs in the present series of experiments were kept in the room where the chemical tests are made and were watched day and night for at least the first 5 days following operation.

The theoretical considerations outlined above seem to be useful in explaining the effect on nerve irritability of various salt solutions when injected intravenously. They also appear to harmonize in a rough way with the findings in tetany and to account for the therapeutic effect of certain solutions. It is not maintained, however, that the disordered salt equilibrium (*i.e.* decrease in calcium, increase in phosphate, etc.) is the underlying disturbance after parathyroidectomy. In fact, many signs seem to point to a fundamental disturbance in protein metabolism, even though evidence in favor of the accumulation of any one toxic protein decomposition product in the blood is as yet incomplete. An observation made in these experiments which suggests a relationship between muscular exercise and tetany may have some bearing on this phase of the question. On two separate occasions attacks of tetany were brought on in a parathyroidectomized dog, which, at the time, gave no evidence of hyperexcitability and, in fact,

seemed on the road to recovery by running 1 to 2 hours on a treadmill.

Further work on this subject should be devoted, we believe, to studying the disordered protein metabolism and the connection between protein metabolites and salt equilibrium. In this field, Watanabe has recently published some interesting experiments, among which are those showing a decrease in the concentration of calcium in the blood after guanidine injections.

CONCLUSION.

The effects of parathyroidectomy upon the calcium, sugar, combined carbon dioxide, and H ion concentrations of the blood have been studied.

The previously observed calcium deficiency in parathyroidectomized dogs is verified, but no support is found for theories based on a disturbed acid-base equilibrium.

General theoretical considerations are outlined which may be of some value in explaining the relationship between tetany and the relative concentration of certain ions in the blood.

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ACUTE HÆMATOGENOUS OSTEOMYELITIS *

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IN acute hæmatogenous osteomyelitis in children primary operation with removal of only sufficient cortex to allow adequate drainage followed by thorough post-operative Dakinization, will frequently preserve the remaining cortex often seemingly dead. Moreover, deformity may be prevented and the period of disability shortened. Care must be taken to avoid injury of the blood supply by unnecessary curettage and packing. Our animal experiments in chemically produced osteomyelitis have suggested the possibility that any necrotic bone, if sterile, will eventually be utilized as a framework for new bone production. The war has made the problems of chronic and traumatic osteomyelitis prominent. Little, however, has been written of the acute hæmatogenous variety prevalent in children.

Bone infections among children differ from those in adults, as the epiphysis is not yet united to the diaphysis and, therefore, the problems of therapy necessarily differ. The infection is believed by many to start in the metaphysis near the epiphysis, and then may spread either throughout the medullary cavity or Haversian canals to beneath the periosteum. It may extend to the neighboring joint by being diverted by the epiphysis through the cortex, where it travels under the capsule, or it may penetrate the epiphysis and reach the joint by this channel.

Lexer has well demonstrated the circulation of the long bones in children with radiograms by injecting the arteries with substances resistant to the X-ray (Fig. 1). His work shows very clearly that with the exception of the circumferential lamellæ, the diaphysis is almost entirely supplied through the nutrient artery, while the epiphysis and neighboring portion of the metaphysis receive an abundant blood supply from the numerous metaphyseal arteries. It is in the relatively avascular zone between the diaphysis and metaphysis (Fig. 1, c) that infection probably starts, and it is along this zone that separation frequently takes place when a sequestrum develops. It is interesting to note that the main nutrient artery entering the shaft courses away from the growing epiphysis which is most frequently involved in osteomyelitis.

In 1919 I attempted to reproduce osteomyelitis in dogs before the students of the third-year course in regional surgery at Columbia. At the suggestion of Dr. William Clarke, of the Laboratory of Surgical

* Read before the New York Surgical Society, March 23, 1921.

Research, through a drill hole in the cortex of the medullary canal of the humerus, croton oil was introduced in glass capillary tube containers having their ends sealed with agar-agar. The hole in the cortex was then plugged with bone wax, and the soft parts and the skin were sutured. By this procedure, repair, following the operative trauma, was allowed to progress before the croton oil was liberated from the capillary tube, probably by the solvent action of the cells and body fluids upon the agar-

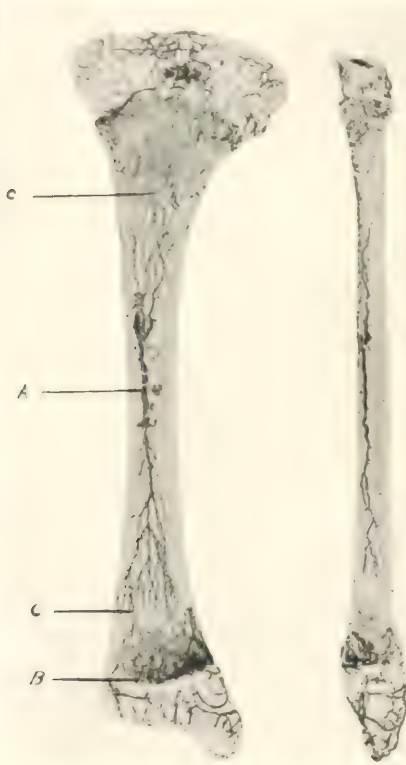


FIG. 1.—Circulation of infant's tibia and fibula. (After Lexer.) A, nutrient artery; B, metaphyseal and capsular arteries; C, relative avascular zone where sequestrum separation usually occurs.

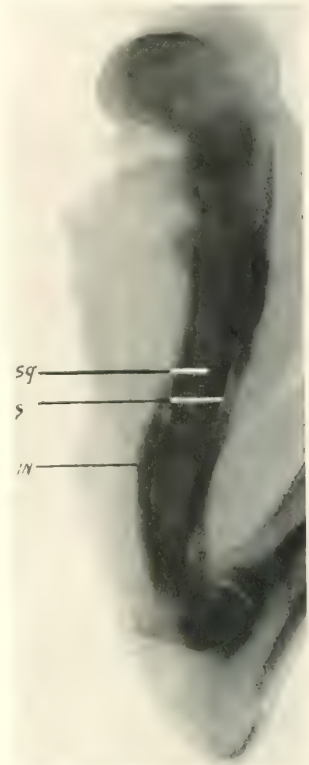


FIG. 2 (Path. No. 5665).—Operation, October 10, 1919. Procedure: Capillary tube containing croton oil inserted in medullary canal. Result: Killed November 3, 1919. Sq, sequestrum; In, involucrum; S, separation zone.

agar. As croton oil causes marked necrosis of the surrounding bone, we were able to produce a chemical osteomyelitis. A sequestrum often 5 to 10 cm. in length and including the entire circumference of the shaft frequently occurred. This sequestrum was separated from a newly formed involucrum by a zone of débris and leucocytes; therefore, all the factors of an acute osteomyelitis were present with the exception probably of bacteria and their by-products. Sections show the sequestrum with an involucrum surrounding (Figs. 2 to 7) but separated from it by a zone of pus. The cortical bone of sequestrum shows absence of nuclei and

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throughout its cancellous portion there is a marked infiltration of leucocytes. The involucrum consists of newly formed subperiosteal bone.

In the prolonged animal experiments radiographic studies show the gradual disappearance of the sequestrum (Figs. 8 to 10), so that at the end of two months it was impossible to detect its former outlines by X-ray. Microscopical sections (Figs. 11 and 12) taken at this time show the disappearance of the zone of separation, and the former sequestrum is now united to the living bone by blood-vessels entering the Haversian

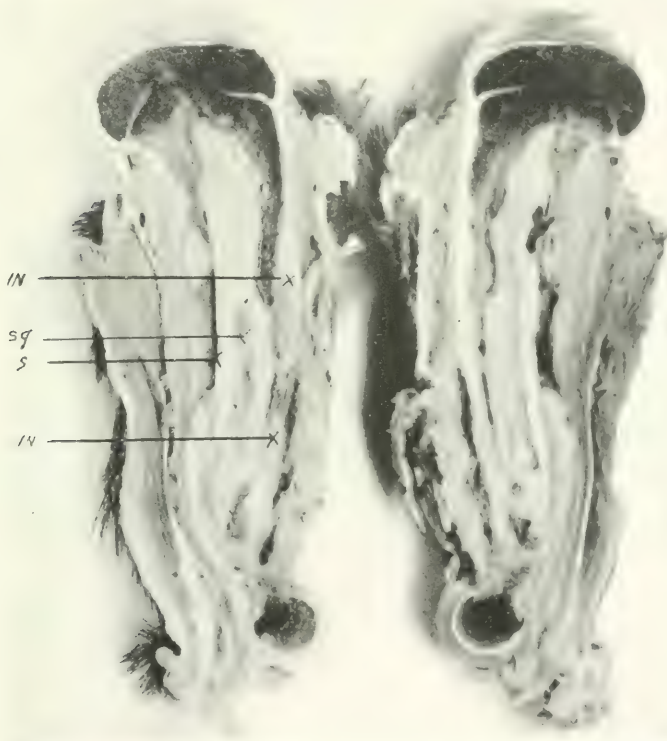


FIG. 3. Path. No. 8033. — Pathological changes in the bone of a dog after the removal of the sequestrum. The involucrum is almost the entire length of shaft. *Sq.*, sequestrum; *In*, involucrum; *S.*, separation zone.

canals. The process is similar to that found in any bone transplant; gradual absorption and deposition of new bone occurring throughout the Haversian canals until all the dead bone has been replaced.

I have emphasized these facts because I believe they have a definite influence on human surgery. I shall show in the study of clinical cases that in children bone tissues that are apparently dead can be saved to advantage.

During the last five years we have had eleven cases of acute osteomyelitis in children on Doctor Pool's service at the New York Hospital. It has been possible to follow these cases and to observe the results of

treatment. Trauma was the most prominent etiological factor in our series. Six or 60 per cent. received injuries varying from ten hours to two weeks before the onset of the acute process. That trauma and the presence of bacteria in the blood-stream can cause osteomyelitis in animals has been demonstrated by Lexer and others. We have produced it in

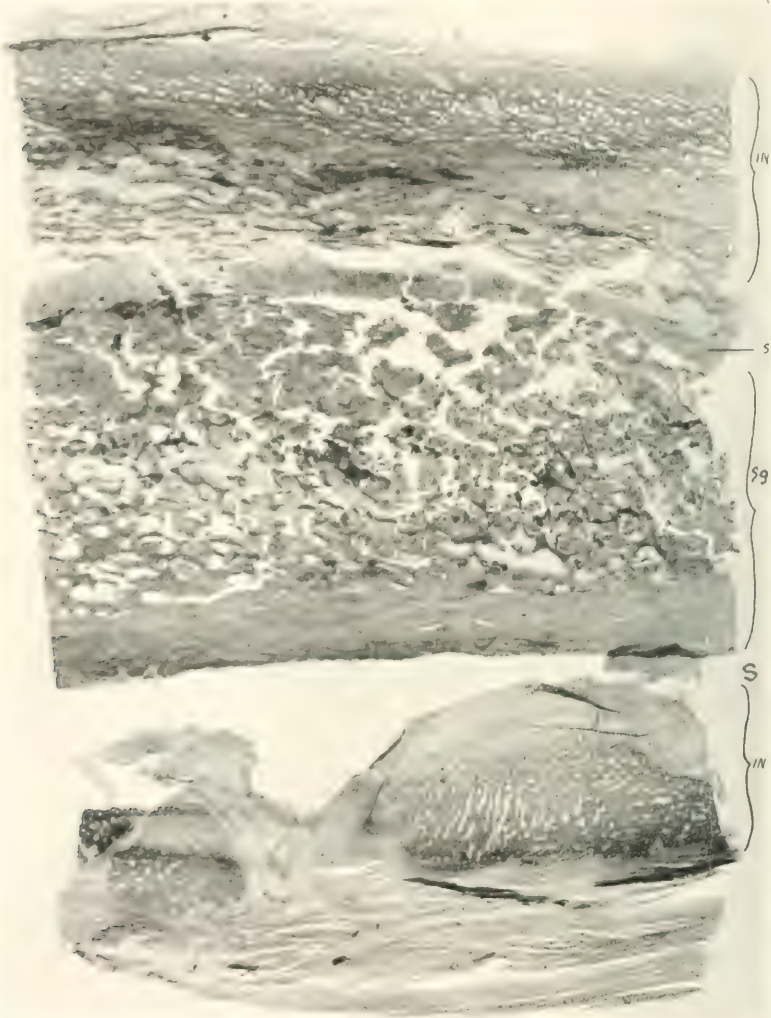


FIG. 4 (Path. No. 5065).—Microscopic section. In the lower zone of separation necrotic debris disappeared during decalcification. *Sq*, sequestrum; *In*, involucrum; *S*, separation zone.

rabbits in the Surgical Research Laboratory by traumatizing the leg without breaking the skin, and injecting into the veins of the ear a strain of staphylococcus from a case of human osteomyelitis, which had subsequently been transmitted through rabbits. On sectioning the femur, which had been fractured by the force of the blow, there was a marked

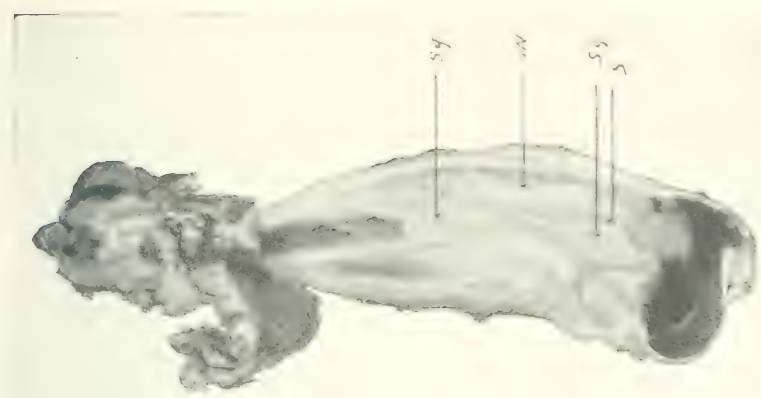


FIG. 1. Illustration of the human torso showing the location of the lungs and heart. The lungs are shown in a light color, and the heart is shown in a dark color. The labels 'sc', 'N', and 'S' are placed near the lungs and heart.



FIG. 2. Illustration of the human arm showing the bones and muscles. The bones are shown in a light color, and the muscles are shown in a dark color. The labels 'sc', 'N', and 'S' are placed near the bones and muscles.

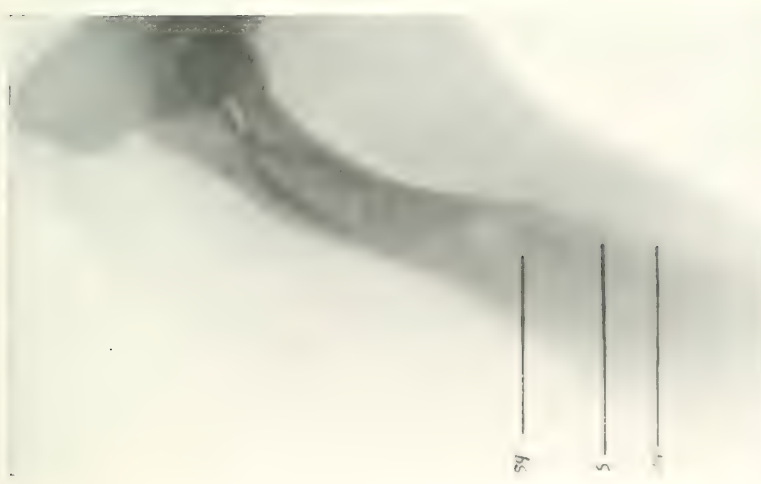


FIG. 3. Illustration of the human leg showing the bones and muscles. The bones are shown in a light color, and the muscles are shown in a dark color. The labels 'sc', 'N', and 'S' are placed near the bones and muscles.

exudation of pus cells at the epiphysis and in the medullary canal. The short period of ten hours, between the time of the injury and the apparent onset of the infection in children, has suggested to me that the disease may be due to bacterial emboli locating in the traumatized small vessels near the termination of the nutrient artery on the diaphyseal side of the

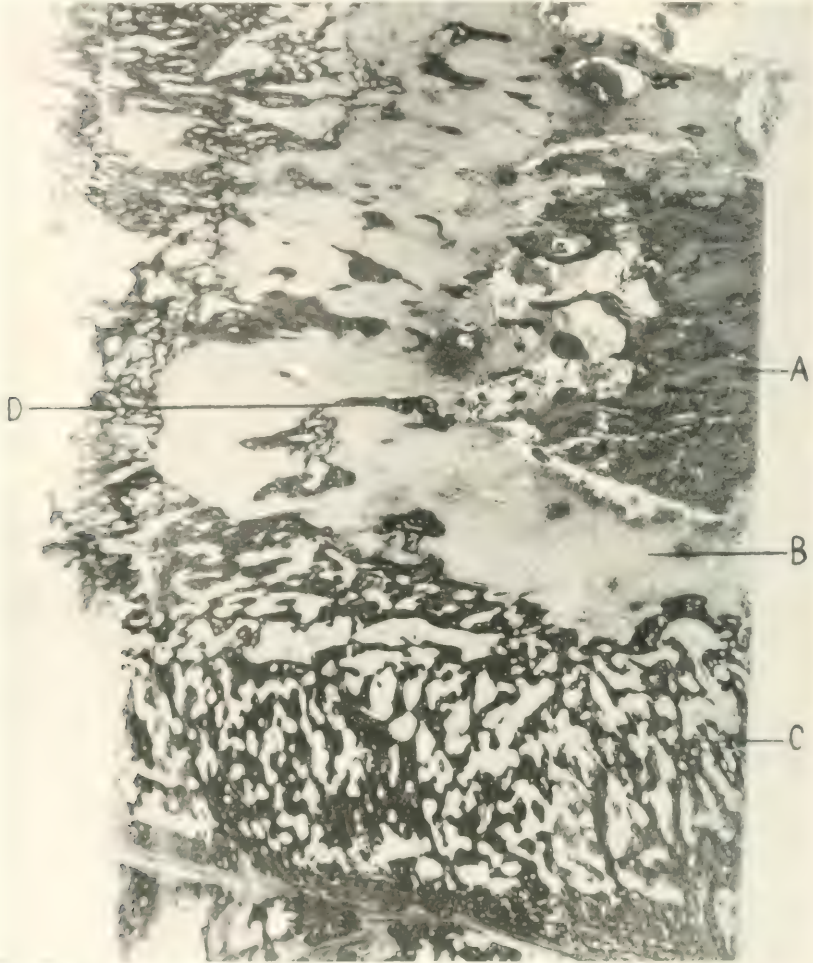


FIG. 1. Section of tibia, showing sequestrum, with surrounding involucrum. A, sequestrum; B, granulation tissue; C, involucrum; D, terminal spicule of bone.

epiphysis (Fig. 1, c). Three cases developed without any history obtainable of previous injury or infection. A recent tonsillitis might be assumed to be the etiological factor in one case.

The tibia was involved five times, four in the upper portion of the shaft and once in the lower. The femur was involved four times in the region of the lower epiphysis. The ulna once at the epiphysis. The neighboring joints were definitely infected in four cases. Metastatic

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joint involvements occurred in one case where the hip on the opposite side and the elbow on the same side were severely infected. One case of double suppurative parotitis developed. Three patients developed metastatic osteomyelitis in long bones in addition to the primary focus. All the patients showed signs of severe infection, high temperature and



FIG. 7B (Path. 6602).—Terminal portion of os parietale showing bone tissue undergoing death, its and gradual reorganisation. A, Dead bone, cell spaces are empty. B, newly formed bone (arrow) surrounding and incorporating dead bone.

pulse-rate, prostration, and all but one case had a high leucocytosis varying from 20,000 to 44,000.

No amputations were done in any of this series.

There was swelling and œdema of the soft parts in ten cases. Bone tenderness on pressure was noted in nine cases and was absent in two cases. Swelling about the neighboring joint was noted in six cases, with limitation of motion in four.



FIG. 8 (Path. No. 5942). - Operation October 10, 1910. X-ray November 10, 1910. Large sequestrum with well-marked involucrum and separation zone. *Iv*, involucrum; *Sg*, sequestrum.



FIG. 9 (Path. No. 5943). X-ray December 1, 1910. Sequestrum and involucrum, but less marked than previous. *Iv*, involucrum; *Sg*, sequestrum.

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FIG. 10 (Path. No. 5042).—X-ray January 15, 1920. No involucrum or sequestrum seen.

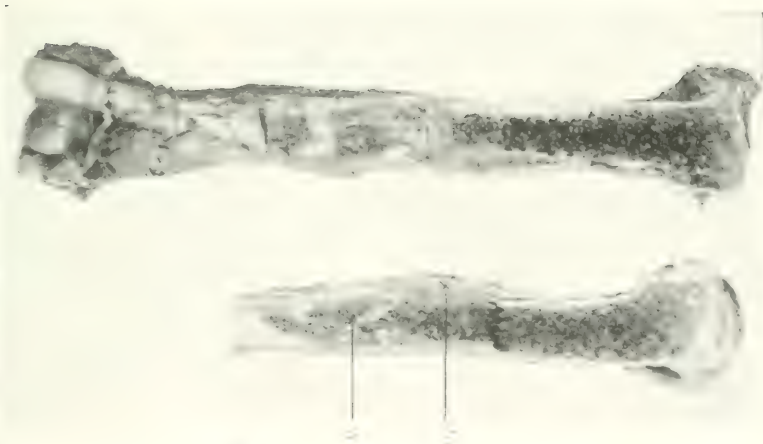


FIG. 11 (Path. No. 5042). Killed January 27, 1920. Photograph of cut section. In subperiosteal bone proliferation; A, probable remnants of old sequestrum, but no separation zone.



FIG. 12. Microscopical section (Path. 5042). Subperiosteal bone proliferation. No zone of separation. A, spaces in which capillary tube lay. B, artifact occurring during decalcification.

There was one death, a boy of seventeen years, with osteomyelitis of the femur, who died twenty-four hours after admission from sepsis and cardiac failure. He had a low leucocyte and high differential count.

Follow-up.—Two cases have been lost track of after having been followed for about two years. One of these at that time had a small persisting sinus, the other was well.

The remaining cases have been followed from one to five years and are well. Two cases with joint involvement where the joint was drained now have ankylosis, one a knee- and the other a hip-joint.

The treatment of acute osteomyelitis in children may properly be divided into the treatment of the acute, and secondly, treatment at the subacute stage. Primary indication for operation at the onset is the relief of pus under pressure, and as such, it should be treated with the same surgical principles as pus collections elsewhere in the body; that is, by adequate drainage, with the least possible trauma and with careful attention to the blood supply. If one considers that frequently periosteum with its blood supply has been stripped from the shaft by the exudation of pus and that the only remaining blood supply to the shaft is through the nutrient artery, one realizes the danger to the entire shaft from too active treatment by curettage or packing.

It is true that in the region of the metaphysis, the bony septa somewhat resembles the septa of the mastoid, and that, therefore, in this region it may be necessary to break up the compartments of the abscess. Care even here should be taken not to traumatize any more than possible.

Simmons, of the Massachusetts General Hospital, has suggested making numerous burr holes through the cortex into the medullary canal as the preliminary drainage. This undoubtedly suffices in certain cases. It is difficult to determine the extent of the process by this method, and with post-operative Carrel-Dakin treatment it is probably more conservative to remove more of the cortex in order to obtain adequate exposure and drainage.

The frequent occurrence of metastatic abscess in the region of the popliteal space, when the lower epiphysis of the femur or upper epiphysis of the tibia is infected, has convinced me that a primary dependent drainage through the popliteal space is in general advisable.

Constant, careful post-operative observation of these cases is necessary, as there are frequent secondary metastatic abscesses in the soft parts. The eventual cure of the patient is due to the careful treatment of the interne performing the Carrel-Dakin technic.

The joint infections frequently showing the presence of staphylococcus are usually amenable to aspiration and irrigation. In our four cases where there was either primary or immediate joint involvement, two cleared up under irrigation and two joints had to be drained. I feel certain that in one of our early cases where the knee-joint was drained it would have been better surgery if aspiration had been attempted.

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In cases where septicæmia and bacteræmia are present, it is necessary to attempt to keep up the nutrition of the patient. In addition to transfusion we have found most advantageous the repeated intravenous injection of commercial peptone as advised by Nolf, of Liège. In one child with streptococcus hæmolyticus blood infection, at Doctor Pool's suggestion, we used this method, with an immediate drop in temperature, consequent improvement in the child's general condition, and within ten days the culture was sterile.

Subacute Stage.—Before the days of wound sterilization the course of a case could be fairly definitely prophesied. At the primary operation, the shaft was opened wide, frequently curetted and packed. Following this, sequestration occurred, frequently involving almost the entire shaft. As advised by Nichols, of Boston, the sequestrum was usually removed at a time when the involucrum was strong enough to maintain the shape of the limb, and yet at such a stage when the involucrum could be inverted, obliterating, as far as possible, the "dead space."

With the introduction of the Carrel-Dakin technic up to date clinically we have had results which correspond to a certain degree with results found in our experimental work. Cases No. IX and No. X of this series show marked regeneration of bone which by either X-ray or gross examination appeared necrotic.

On account of limited space brief summaries of only three illustrative cases will be given.

CASE I.—Girl of eight years of age, admitted May 5, 1915, with history of having fallen and injured her left knee four days previous. She complained of severe pain when she attempted to walk. Ten hours after injury the knee was considerably swollen and the child cried with pain on any motion. Examination revealed a knee-joint markedly red, swollen and exquisitely tender. Active and passive motion practically nil. Some swelling in the popliteal space. The knee-joint was at first operation drained and a quantity of pus obtained. Later she developed an osteomyelitis of the lower end of the femur and several operations were done, removing the necrotic bone and draining the abscesses in the soft parts. Following the fourth operation she received a fracture at the epiphysial line and marked displacement (Figs. 13 and 14). During this time she had been extremely ill, with a very high temperature, and her recovery at one time was despaired of. On leaving the hospital she had a shortening of two and one-half inches, fixation of the knee-joint and persistent sinus. At the present time she still has a shortening of two and one-half inches, but otherwise is perfectly well, is able to run, dance, and has not had a sinus for over three years.

Comment.—This patient, with a marked deformity and necrosis of the shaft, attained a very satisfactory functional result; new bone proliferating in such a manner as to change the lines of force and give her a straight leg.



FIG. 14.—Clinical case No. 1, June 5, 1916. Shows reformation of bone. No sinus.



FIG. 15.—Clinical case No. 1 (see case history). Marked destruction of shaft with the fracture at the epiphysal line and displacement, July 12, 1915.

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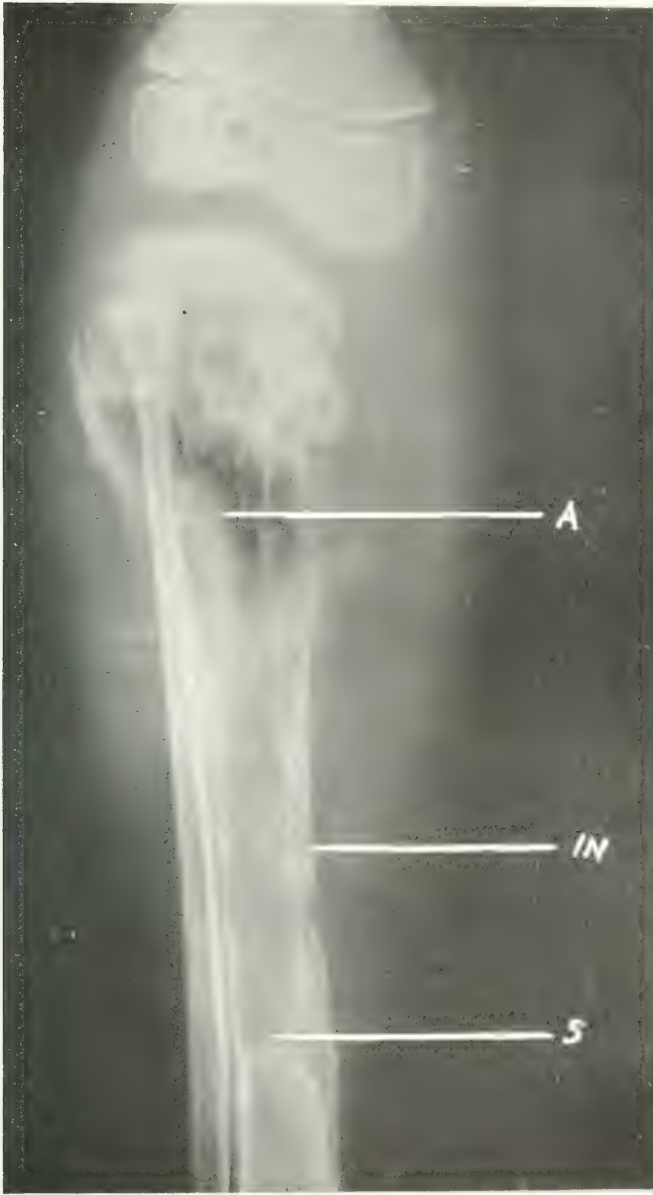


FIG. 15.—Clinical case No. 9. X-ray July 30, 1910. Operation June 22, 1910. Removal two inches of anterior surface upper third of tibia. A, area of bone removed at primary operation; In, involucrum; S, separation zone.

In Case IX (Figs. 15 to 18), a girl of five years, who came into the hospital with an acute osteomyelitis involving the upper third of the tibia, drainage was established by removing the anterior part of the cortex in the upper third. Later X-ray showed a marked rarefaction and apparent sequestrum formation in the lower third. As her temperature was approaching normal, and her condition



Fig. 10.—(Continued) from No. 9. Operation July 22, 1919. X-ray, August 22, 1919. S, former separation. Marked subperiosteal proliferation. No operative procedure has been performed on this area.

quite satisfactory, it was considered advisable to delay operation upon the lower third. Later X-ray showed subperiosteal bone proliferation around this zone of separation, and an X-ray one year later showed a relatively normal appearing shaft. At the present time she is well, without any sinus, and apparently the process is cured.



FIG. 17. Clinical case No. 9. Operation July 1906. Case 10. (See text.)

Comment.—Primary radiographic studies of this patient showed the appearance of rarefaction and sequestration in the lower third of the tibia. This completely disappeared without any operative interference.

Case X (Figs. 19 to 22), a boy seven years old, who elsewhere had been insufficiently drained for an acute osteomyelitis of the tibia.

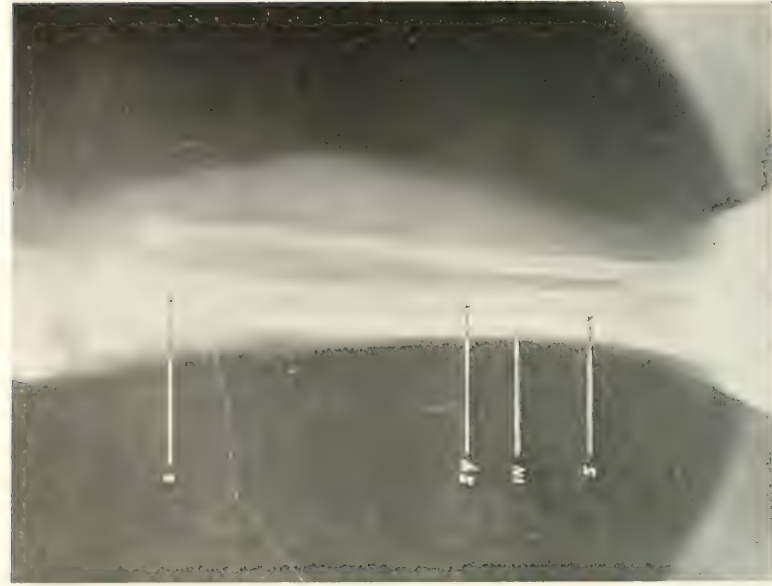


FIG. 19.—Clinical case No. 10. X-ray December 8, 1919, previous to operation. *Sy.*, sequestrum; *I.n.*, involucrum; *N.*, separation zone.



FIG. 18.—Clinical case No. 9. Operation June 22, 1919. X-ray November 24, 1919. No sinus. Patient apparently well.

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came into the hospital extremely ill, with a temperature of 106° , marked leucocytosis and prostration. At the primary operation the entire anterior portion of the cortex of the tibia was removed. There was a fracture of the upper third due to the complete destruction of the bone. Periosteum was separated by pus from the greater part of the shaft. In this case Carrel tubes were inserted posteriorly between the necrotic shaft and the periosteum. The shaft appeared dead. It was not removed because it was thought advisable to maintain this portion of the shaft to prevent deformity. This was

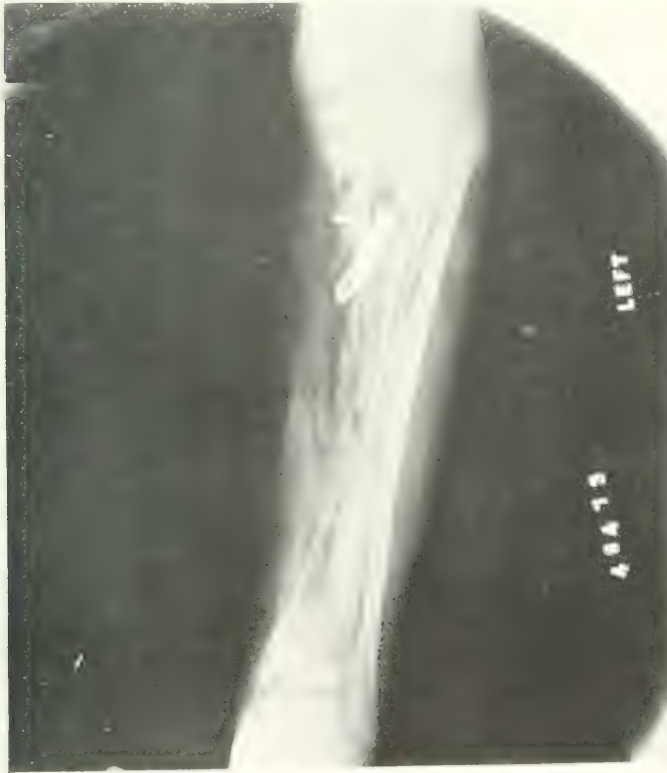


FIG. 20.—Clinical case No. 10. X-ray February 7, 1920. Operation December 9, 1919. Anterior surface of the cortex of the tibia removed. Drainage tube in popliteal space shown. See case history.

the child who had a streptococcus hæmolyticus blood infection and was treated with intravenous injections of peptone. After about five weeks, granulations were seen springing up on the surface of the formerly necrotic shaft. X-rays taken two months after the primary operation showed new bone formation about and apparently incorporating the remnant of the old necrotic shaft. At the present time the patient has a small discharging sinus in the upper third, but the X-rays showed marked new bone proliferation without the sign of any sequestrum.

Comment.—This patient, who was too sick to stand any opera-



Fig. 10. New base position about and incorporating former dead shaft.

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FIG. 22.—Clinical case No. 19. X ray (1) taken 18. 1905. The osteomyelitis was small, but it was third, otherwise healed. Patient walking on leg. (2) taken 1906.

tive procedure, had a dead shaft exposed in the wound. After Dakinization, granulation tissue appeared on the former necrotic surface. The bone was later incorporated and the new bone formed about it.

Whether or not in this case the sequestrum was sterilized by the Dakin solution it is difficult to state, but it appears as if it were acting very much as the chemical sequestrum produced by croton oil injections in the experimental laboratory.

Finally, because the whole problem is unsolved concerning the changes which take place in bones, seemingly dead, in the process of repair, this is not a consideration of biological bone changes. These statements are observations of clinical facts, conclusions upon operative findings, and subsequent results of Dakin treatment.

Therefore, from the experience obtained by these cases and from the many animal experiments, I am convinced that in the future in the treatment of children, we can be more conservative, as follows:

First. Adequate drainage should be obtained with as little trauma as possible.

Second. In cases where the patient is clinically progressing favorably, bone, which by X-ray or gross examination appears dead, may frequently be saved to advantage in order to prevent deformity and hasten convalescence.

BONE REPAIR FOLLOWING INJURY AND INFECTION *

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Since McEwen's classical work on bone repair, there has been much uncertainty in the minds of clinicians regarding the process that occurs in bone repair following injury. Whether or not the periosteum is the all-important factor in osteogenesis has clouded our minds. The significance of the bone cell, of the periosteum, and the significance of intermembranous or of intercartilaginous bone development is not known. The terms after long usage are established as entities, thus tending to suggest biologic differences because of microscopic difference. Until the physical chemist gets at the root of things, confusion concerning bone in all parts of the body will exist in the minds of laboratory workers. I believe when the real secrets of bone formation are understood, we shall acknowledge that osteogenesis occurs in the same manner in all tissues. The tissues that are seemingly different under the microscope, I believe, are chemically similar whenever osteogenesis occurs, be it repair in a fracture or repair following infection, be it in periosteum, in muscle planes, in artery wall or in the ventricular septum of the heart. Stop and think of the confusion which necessarily follows, when at best only microscopic sections can be seen of the various complex tissues manifesting bone formation at single stages of each experiment. The physiologic chemist is handicapped in the same manner because his analysis by necessity is of a single stage, always involving many tissues. In the human being, and in the laboratory animal used for experiment, the tissues are far too complex in their functional activities and structural make-up to make it possible for the observer to deduce what happens in single cells such as may be present in osteogenesis; hence, the confusion among experimenters as expressed in the literature. The surgeon is too likely to feel that he does not know much about bone repair because he is so confused by the differences of opinion of the various experimenters. Those interested in osteogenesis are as often as not disputing over names and terms rather than discussing processes, and bone formation is truly a process and not a state.

* From the Laboratories of the Department of Surgery, Columbia University College of Physicians and Surgeons.

* Read before the Annual Meeting of the Colorado State Medical Society, Pueblo, Oct. 6, 1921.

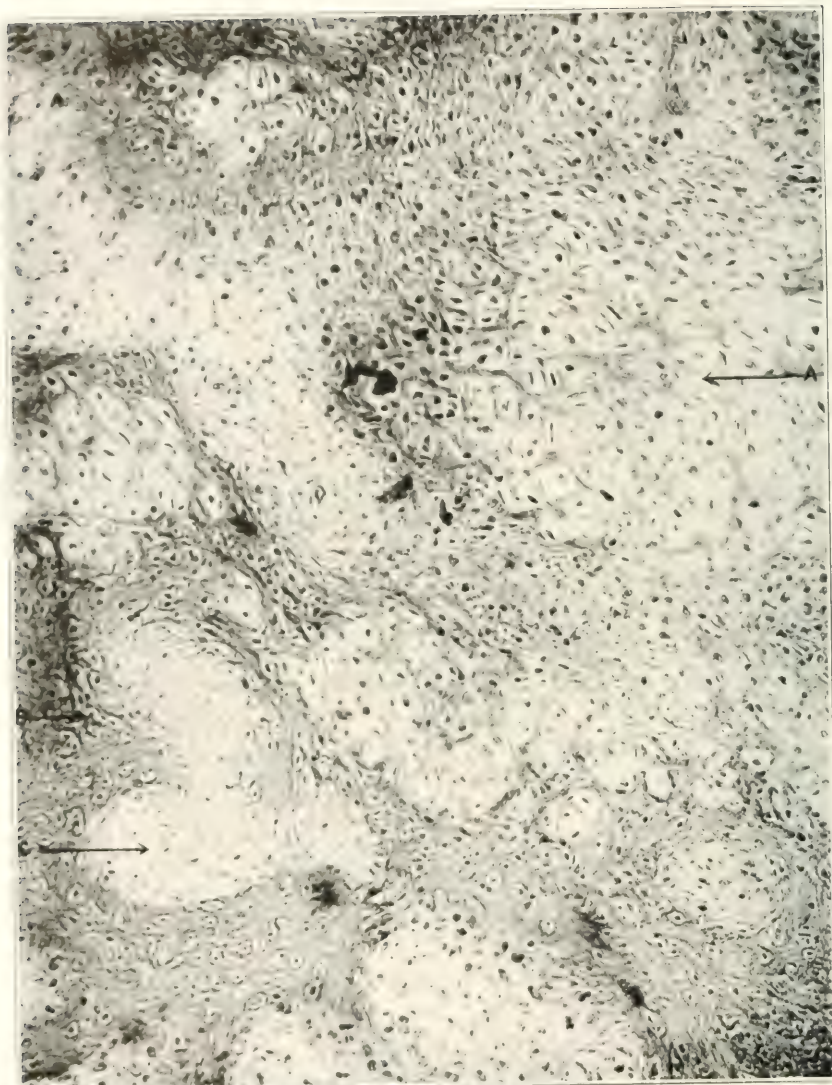


Fig. 1.—Early bone formation following fracture: *A*, cartilage; *B*, new bone; *C*, connective tissue. Gradual transitions are observed from connective tissue to cartilage, from connective tissue to bone and from cartilage to bone. No distinctive cells are seen.

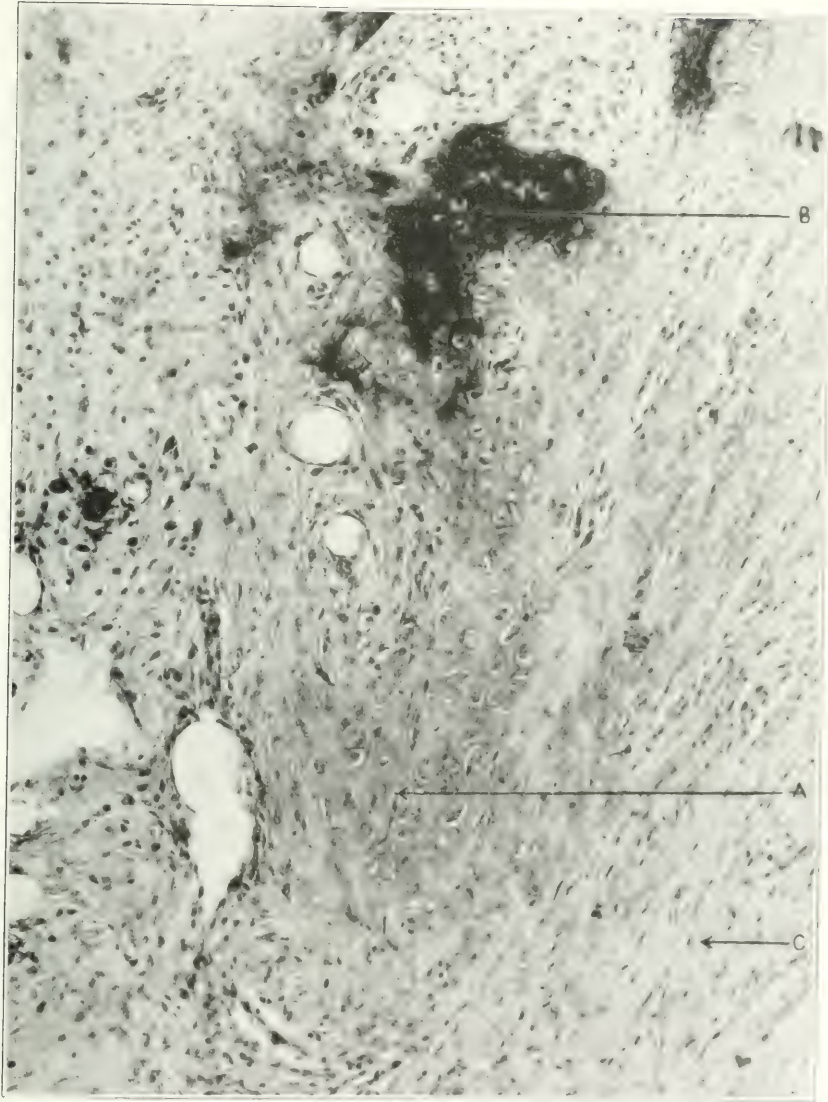


Fig. 2.—Scrapings removed from fractured humerus of a human being, twelve days after injury: *A*, fibrocartilage; *B*, early bone; *C*, connective tissue.

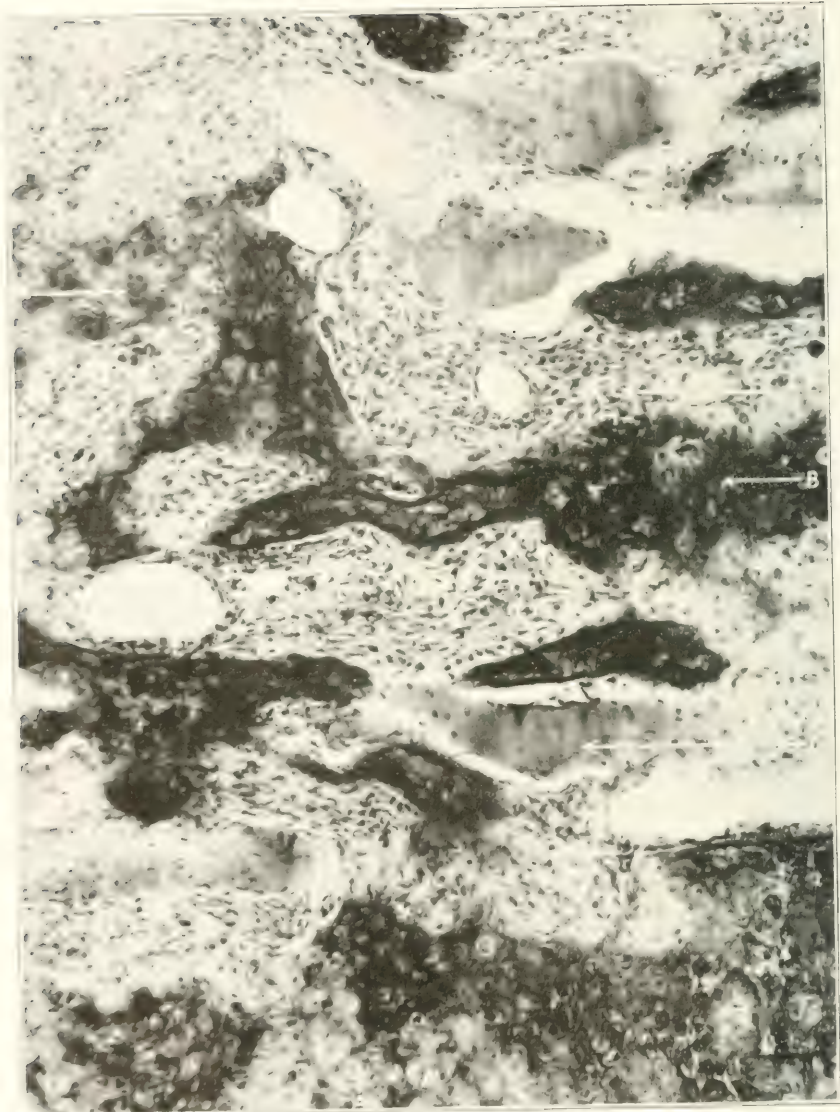


Fig. 3.—Ossification occurring in the midst of muscle fibers, twelve days following a fracture of the humerus in an adult: A, ossification occurring in cartilage; B, early bone; C, connective tissue; D, degenerating muscle fibers.

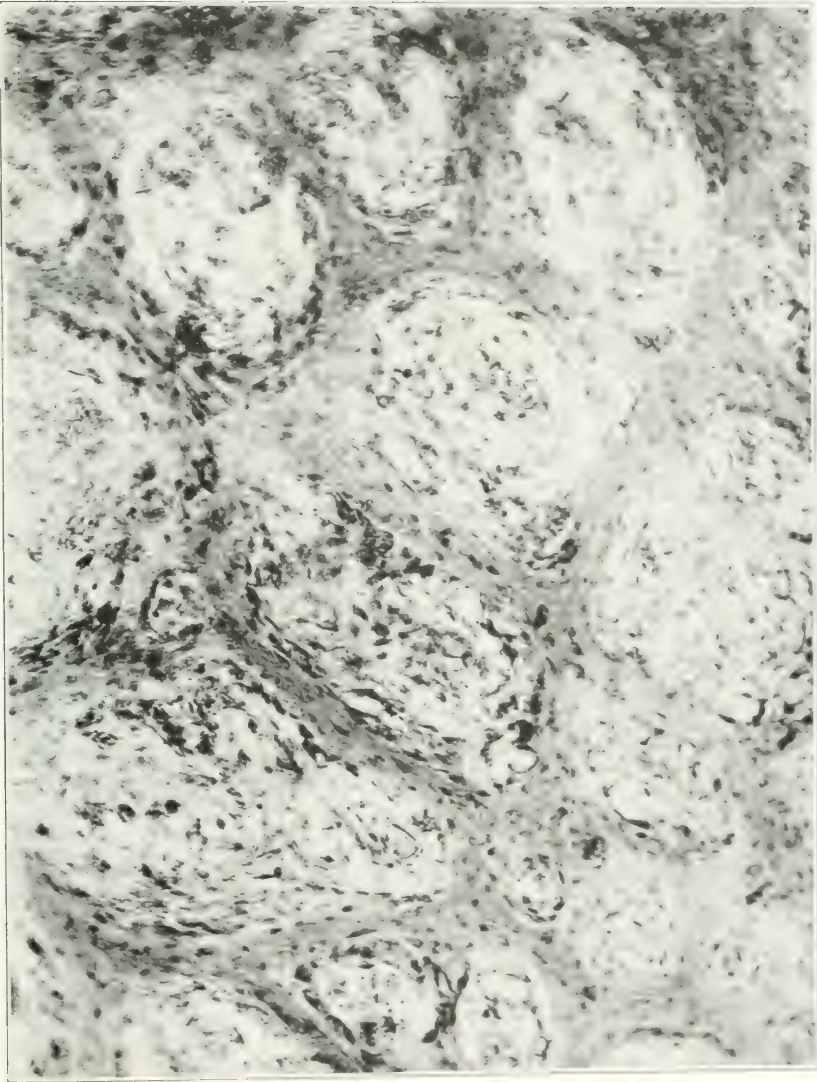


Fig. 4.—Callous formation seventeen days following fracture, showing deposition of calcium salts on the avascular zones in early connective tissue.

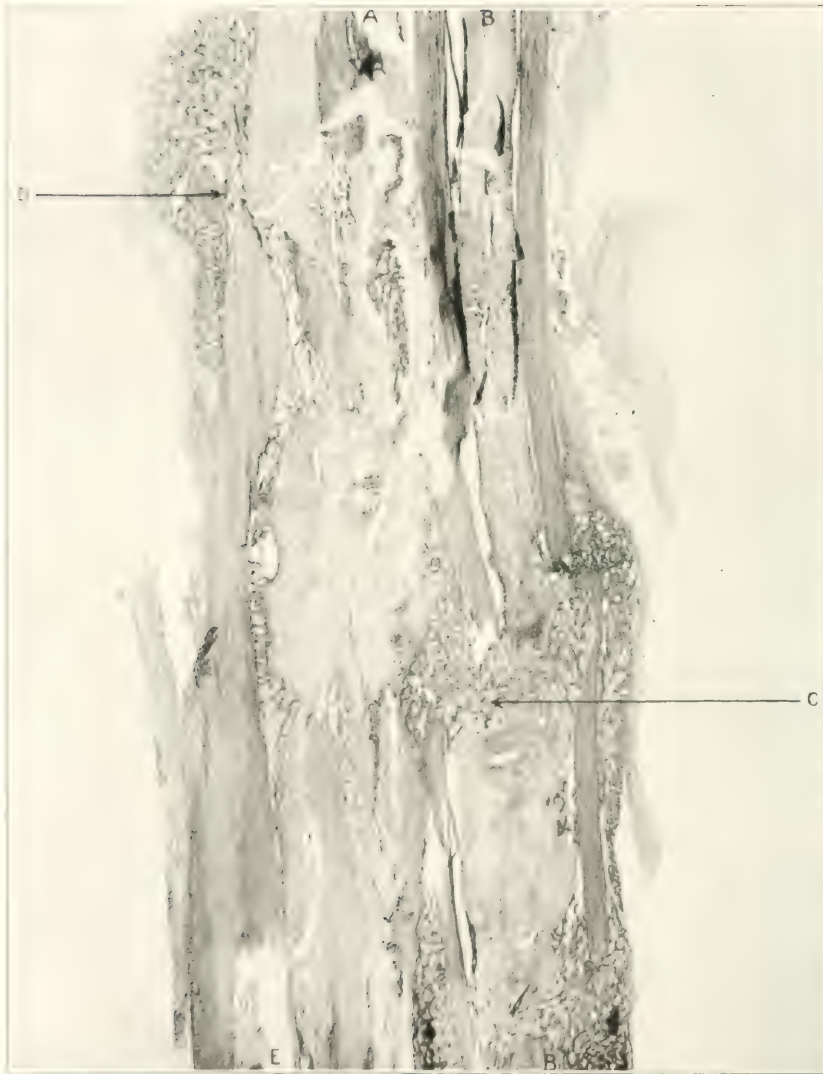


Fig. 5.—Comminuted fracture of radius and ulna in rabbit, fourteen days after injury: *A*, interosseous membrane; *B*, medullary canal of radius with cortex on either side; *C*, new bone forming in connective tissue following hemorrhage around the fractured ends and across the medullary canal; *D*, detached bone fragments surrounded by new bone formation; *E*, medullary canal of ulna.

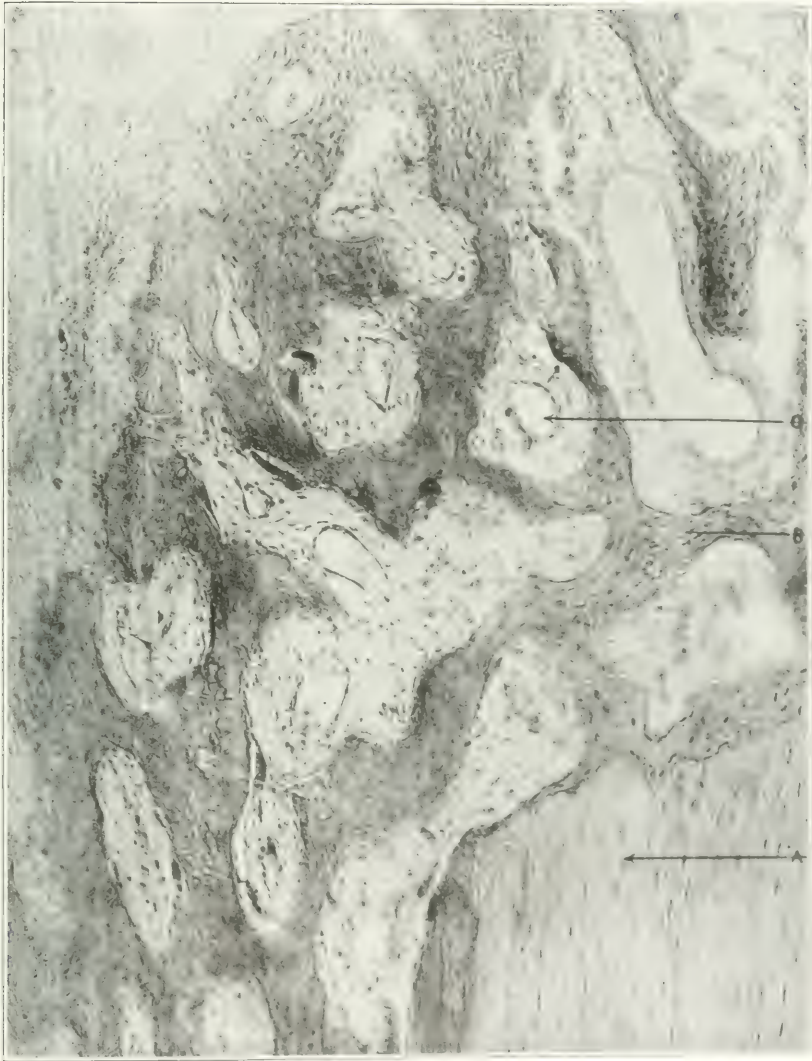


Fig. 6.—High power magnification of radius and ulna shown in Figure 5. *A*, end of fractured shaft showing atrophy at end with absence of bone nuclei; *B*, new bone formation in the connective tissue; *C*, areolar connective tissue with newly formed blood vessels.

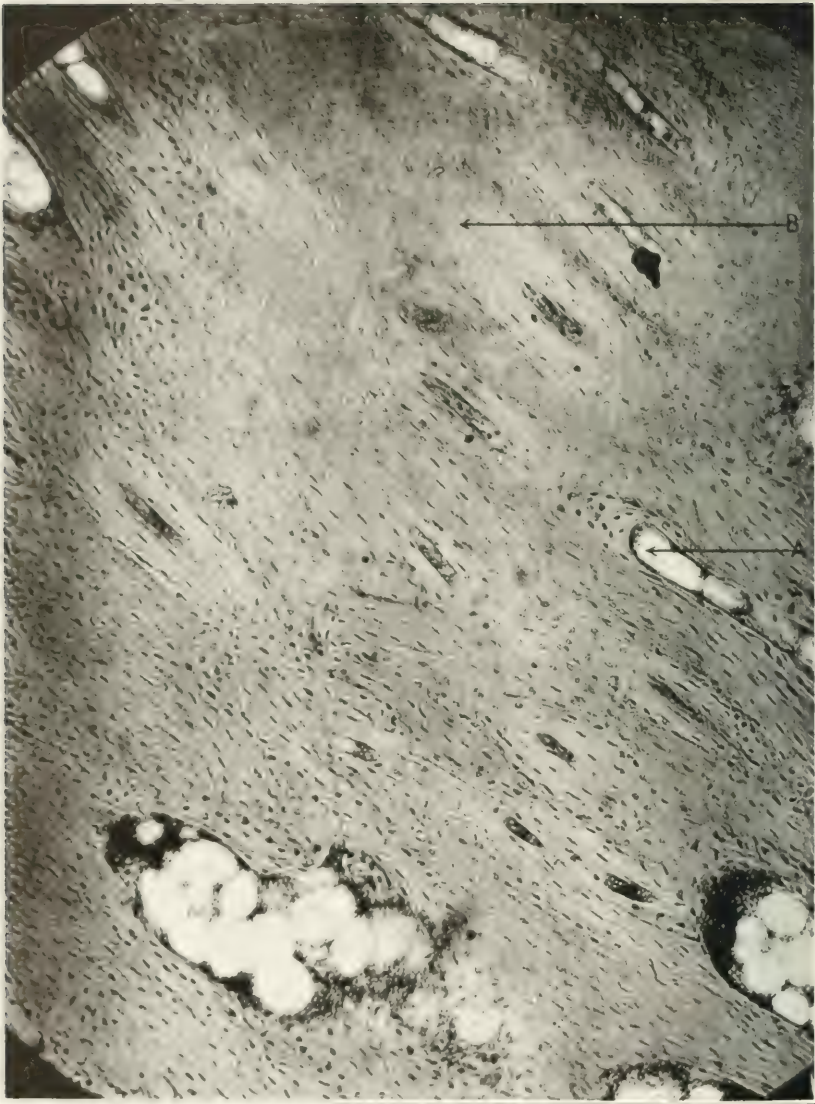


Fig. 7.—Bone transplants four weeks following operation: *A*, haversian canal with reestablishment of blood supply and surrounded by one or two layers of active bone nuclei; *B*, absence of nuclei in bone distant from haversian canal.

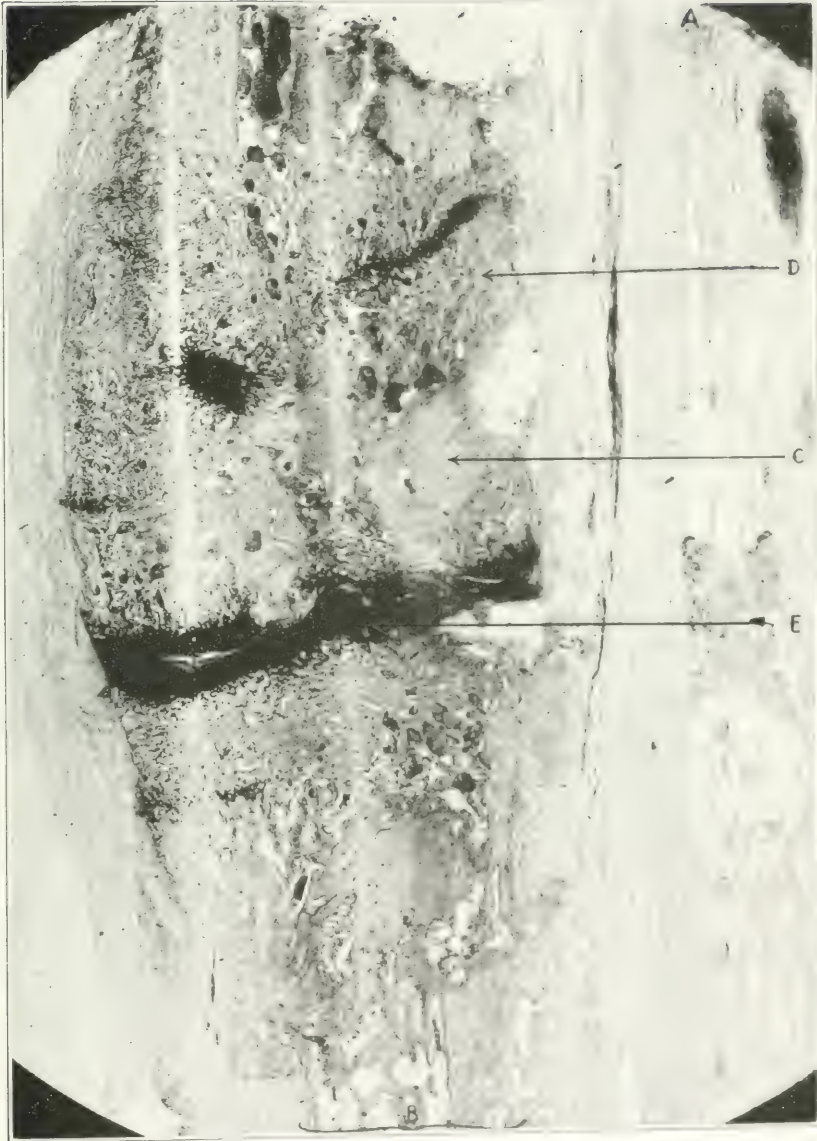


Fig. 8.—Transplantation of bone fragments to rat (series 14) after following operation: *A*, ulna; *B*, radius; *C*, bone fragments; *D*, areas of rarefaction near periphery; *E*, new bone formation about periphery of fragments; *E*, cartilage forming false joint.

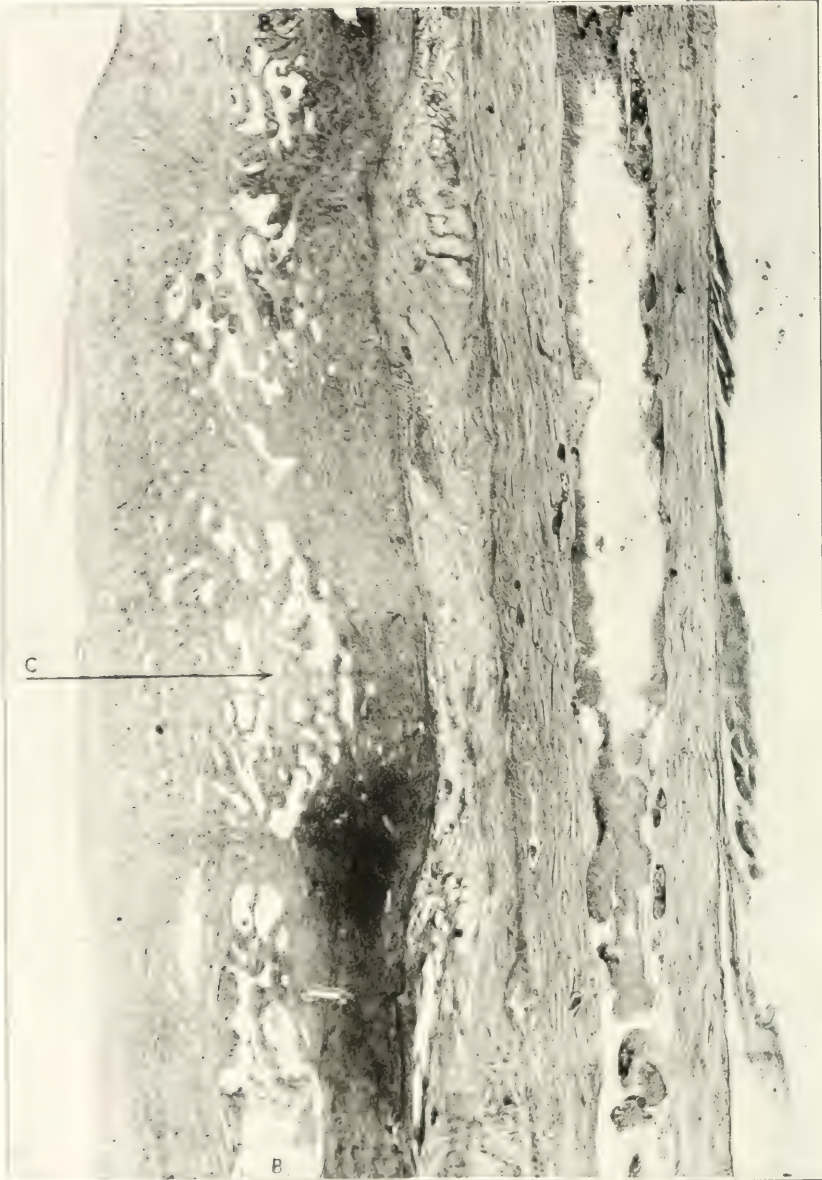


Fig. 2.—Transplantation of bone fragments to fill defect in radius, 347 days following operation: *A*, ulna; *B*, radius; *C*, beginning formation of medullary canal. The entire zone shown in the illustration is the area in which the transplants were placed. It is no longer possible to detect the fragments; but a new cortex and medullary canal are being established by the gradual absorption of the fragments and the formation of new bone.

In order to have satisfactory therapeutic results, it is advisable to accept some practical working theory that will cover all types of bone formation. This theory should be broad enough not only to cover the skeletal bone formation but also the extraskeletal bone formation

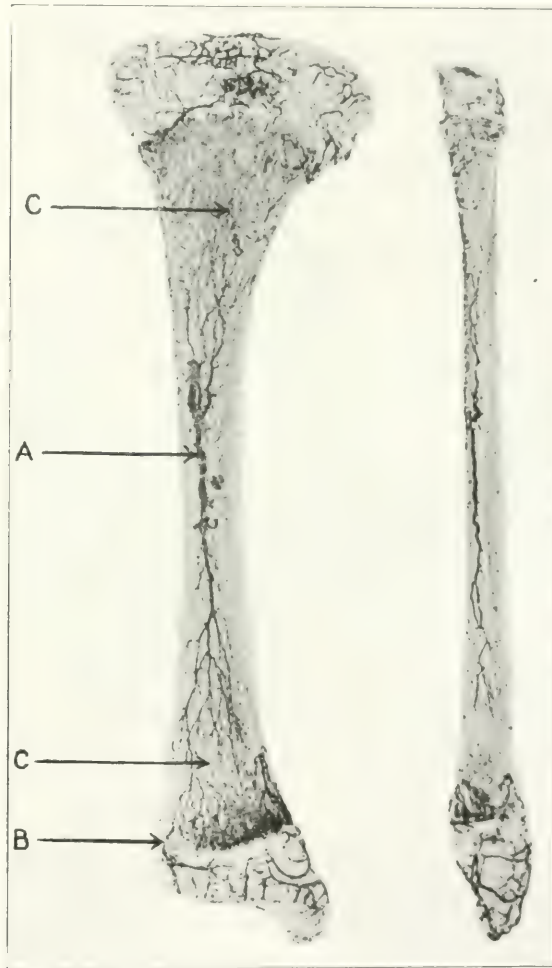


Fig. 10.—Circulation of infant's tibia and fibula (after Lexer): *A*, nutrient artery; *B*, metaphyseal capsular artery; *C*, relative avascular zone, where sequestrum separation usually occurs.

that occurs in so many places in the body. Extraskeletal bone formation occurs in one or more tissues in all of us if we live long enough, and it may be produced experimentally in animals without difficulty. Extraskeletal bone occurs frequently in man in the arterial wall and

in the muscles. It has been described as having been found in nearly all of the tissues of the body, such as the lymph nodes, ovaries, kidneys, fascial planes and wall of the orbit.

Experimentally, bone has been produced in animals by ligating the vessels of the kidney and wrapping the omentum about it. Microscopic sections of this kidney from one to two months later show areas of true bone and calcification occurring in the parenchyma. Neuhoff,

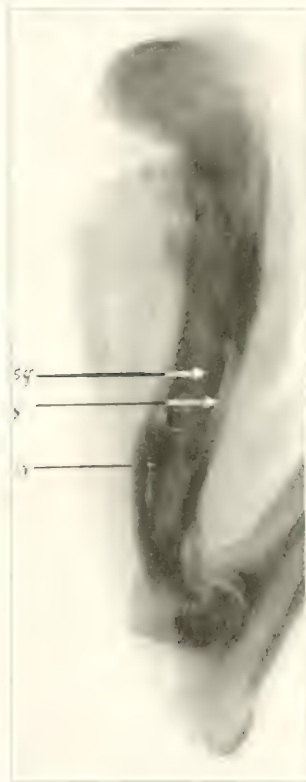


Fig. 11.- Roentgenogram of humerus, Nov. 3, 1919. Croton oil was inserted into the medullary canal in capillary tube containers, Oct. 10, 1919: *SQ*, sequestrum; *In*, involucrum; *S*, separation zone.

working in the laboratory of surgical research at Columbia University, found bone almost universally in fascia lata transplants that he had made to fill a defect in the bladder. Any theory, therefore, that we may accept should be broad enough to explain these irregular types of bone formation as well as the repair of bone following fractures and infection. We may, for the sake of discussion, classify the theories of bone repair roughly into three groups: (1) periosteal; (2) osteoblastic, and (3) extracellular deposition of calcium salts.

1. The periosteal theory presupposes that the periosteum and endosteum are definite organs for bone formation and repair, and that the bone cells arise from them and from no other source.

2. The osteoblastic theory may be divided into two subtitles.

Type A. This assumes that in bone repair following injury bone cells are liberated from their lacunae and that they reproduce and form new bone.



Fig. 12.—Cross-section showing massive sequestrum extending almost the entire length of the shaft; *SQ*, sequestrum; *In*, involucrum; *S*, separation zone.

Type B. This assumes that following injury wandering connective tissue cells, fibroblasts, are drawn into the area of trauma. Owing to the stimulus of the repair, they are transformed into bone producing cells and then become specific cells.

3. The extracellular deposition of calcium salts theory assumes that there is no definite bone producing cell; that following injury, possibly by positive chemotaxis, calcium salts in the proportions usually found

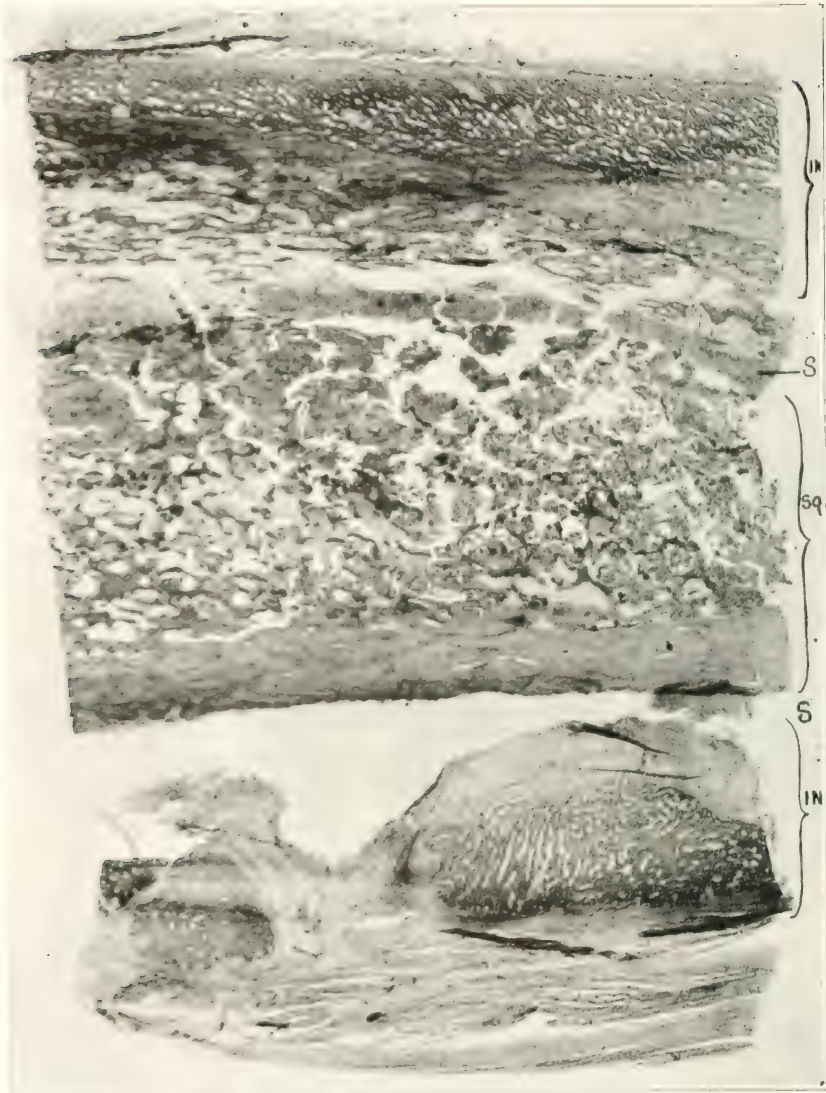


Fig. 13.—Microscopic section: *Sq*, sequestrum; *In*, involucrum; *S*, separation zone. Under high power magnification the bone nuclei in the sequestrum are absent and the zones in the medullary canal are filled with leukocytes. The separation zone *S* contains debris and numerous polymorphonuclear leukocytes. In the lower separation zone *S*, debris disappeared during the process of decalcification.

in bone are deposited in the extracellular frame-work of connective tissue and that the connective tissue cell then becomes a bone cell by functional adaptation.

Any one of these three theories may explain the ordinary repair of bone as seen in fractures; but it is difficult to explain under the periosteal theory the formation of extraskeletal bone.

The bone in fascia lata transplants in the bladder found by Neuhoff cannot be explained by the periosteal theory, and it is difficult to explain

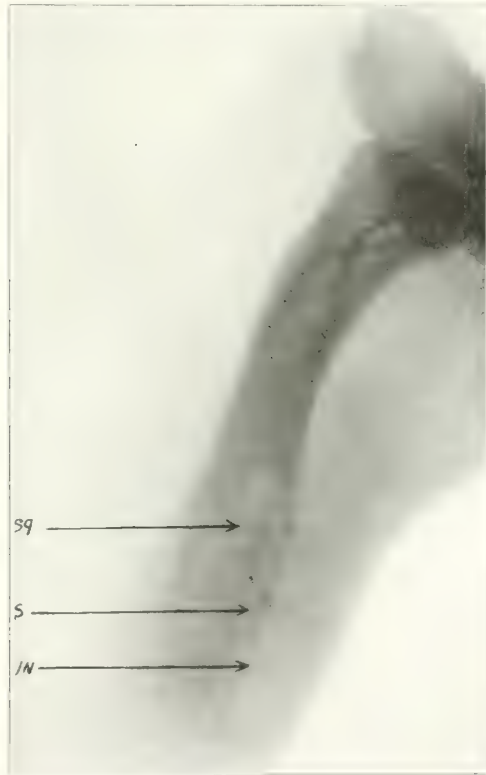


Fig. 14.—Following insertion of capillary tube containing croton oil, in medullary canal, Sept. 21, 1920. Roentgen ray. Large sequestrum in upper half of humerus, Oct. 15, 1920.

it if we assume that the osteoblast is a specific cell coming from other bone cells. Moreover, it is impossible to explain the formation of bone in the arteries of human beings, in the lymph nodes or in the kidney by either of these theories.

If we assume that bone is formed by metaplasia of connective tissue cells into osteogenetic cells or if we assume that it is purely a chemical deposition in living connective tissue, we may explain the phenomenon very easily.

The third theory has seemed more plausible to me. Gideon Wells has shown that if cartilage is transplanted into the omentum it has a greater power of absorbing calcium from the blood than has any other tissue similarly placed. He believes that the same proportions of calcium phosphate and calcium carbonate are present in the ash of calcified material as bone, the main difference being that calcification occurs in dead tissue while ossification occurs in the presence of living tissue. In sections of kidneys in which the vessels have been ligated,

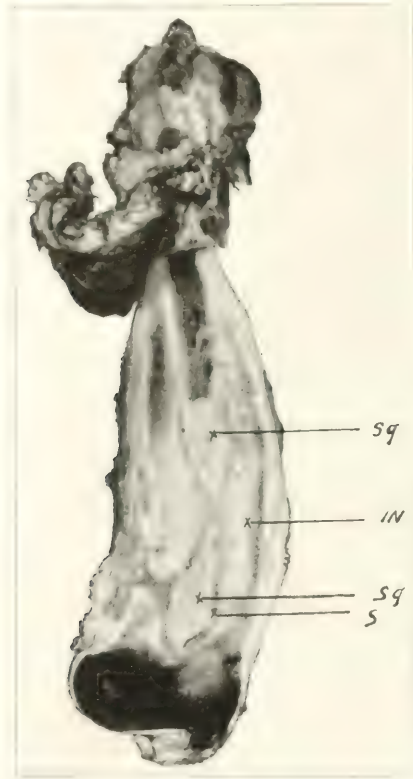


Fig. 15.—Cross-section showing massive sequestrum, with thick involucrum and zone of separation: *SQ*, sequestrum; *In*, involucrum; *S*, zone of separation.

there are zones of calcification and ossification, the calcification occurring in dead tissue and ossification occurring where living bone cells are observed.

The simplest type of bone repair is seen following fractures. In a series of fractures on animals, I have been able to follow the repair at various stages. Immediately following the fractures, there is hemorrhage between the broken ends. Fibrin is then deposited and con-

traction of the clot occurs. In from about five to ten days the organization of the clot by the ingrowth of connective tissue occurs. Connective tissue appears to take a definite lobulated arrangement, so that if we look at a cut section, we find blood vessels and then areas of thin areolar connective tissue (Figs. 1 to 4).

Calcium salts are then deposited in the avascular zones between the blood vessels. Early callus looks very much like the lobules of the

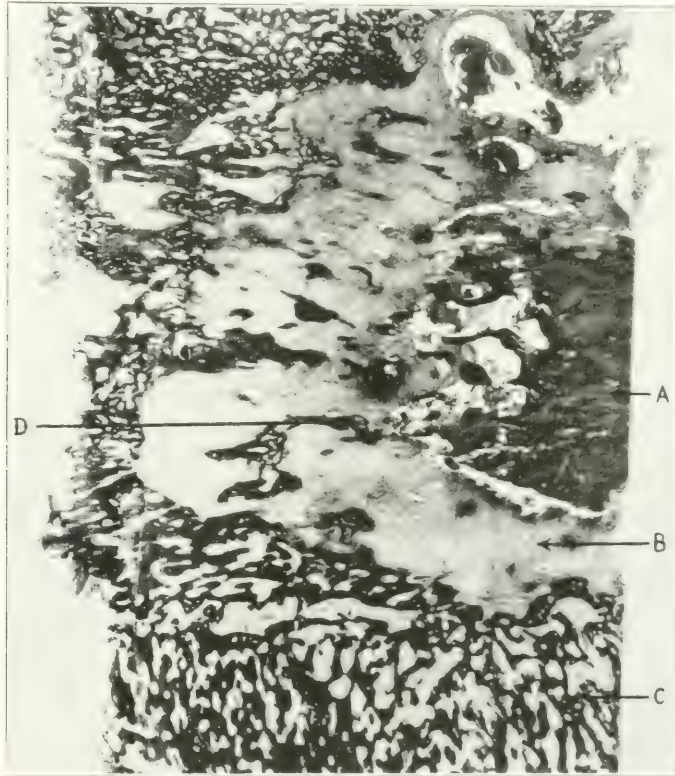


Fig. 16.—Lower power magnification of terminal portion of sequestrum with surrounding involucrum: *A*, sequestrum; *B*, granulation tissue; *C*, involucrum; *D*, terminal spicule of sequestrum shown under high power in Figure 17.

liver. At first the blood vessels appear about this area of areolar tissue and then an area of new bone appears. At a later period, the areolar zone is almost completely replaced by osteogenetic tissue. This process continues until there is a definite haversian canal system of adult bone. In the zones of exuberant callous formation, absorption of the calcium salts takes place and scar tissue results. Bone atrophy occurs almost universally near the fractured ends. A great number of nuclei of the bone cells in the lacunae disappear.



Fig. 17.—Terminal portion of sequestrum showing new bone formation about it, and gradual reorganization: *A*, dead bone, cell spaces are empty showing no nuclear stain; *B*, newly formed bone surrounding and incorporating dead bone.

As the granulation tissue springs from the periphery and the new blood vessels run at right angles to the shaft, the haversian canals as seen by microscopic examination from three to five months following fracture, are perpendicular to the normal haversian canals of the shaft. At the end of a year, however, by a gradual process of absorption and new formation, canals are reestablished in a normal direction. Periosteum, as it is a connective tissue and as it has an areolar layer



Fig. 18.—Large sequestrum, Nov. 10, 1919, with well marked involucrum and separation zone: *In*, involucrum; *Sq*, sequestrum; operation performed, Oct. 10, 1919.

immediately adjacent to the shaft, undoubtedly serves as a bone forming membrane; but it is not the only connective tissue which may form bone (Figs. 5 and 6).

The study of bone grafts shows strikingly why the clinician and the laboratory worker have differed in their accounts of the after-history of the graft.

The clinician has usually stated that grafts "live," because if occasion should arise demanding the performance of a secondary operation,

one finds that the cut section of the graft bleeds and that it has the general appearance of living bone. Roentgenograms also show the graft appearing as normal bone.

The laboratory worker on microscopic examination finds that in grafts of one to two weeks' duration the nuclei do not stain and the bone appears dead. Microscopic examination at a later period reveals the blood vessels reestablished in the haversian canals, and about them one or two layers of living bone cells, while portions of the graft

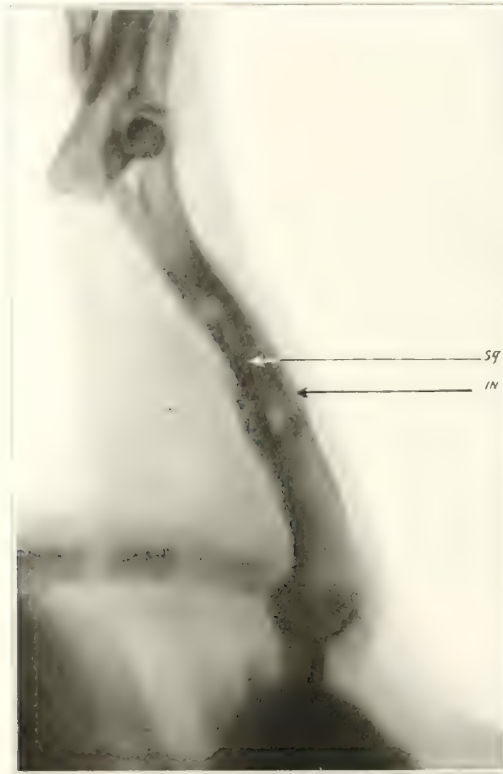


Fig. 19.—Sequestrum and involucrum, Dec. 1, 1919, less marked than previously: *In*, involucrum; *Sq*, sequestrum.

further from the canals show the absence of nuclei (Fig. 7). The process then continues as a gradual absorption of the dead bone and the formation of new bone in its place. It is easy to see that the bone at this period would bleed on section and would appear alive clinically.

In order to have a successful graft, three conditions must be established: First, the graft must maintain the shape of the limb; second, it must have its blood supply quickly reestablished and, third, it must stimulate osteogenesis in the neighboring tissues.

McWilliams, in a thorough analysis of the various methods of bone grafting, read before the American Surgical Association at Toronto in June, 1921, came to the conclusion that the presence of periosteum upon the graft had very little influence upon its ultimate success. He analyzed about 1,390 cases in which grafts had been used. Of these, 1,170, with 82.9 per cent. of successes, had periosteum, while 196, with 82.6 per cent. of successes, were without periosteum. In



Fig. 20.—Roentgenogram, Jan. 15, 1920; no involucrum or sequestrum seen.

analyzing the types of transplants, he found that the successes were relatively as follows: bone pegs, 95.8 per cent.; osteoperiosteal (Ollier. DeLangeniere), 87.3 per cent.; end-to-end (without inlay), 82.5 per cent.; inlay, 80.9 per cent., and intramedullary, 76.6 per cent.

If we study these, we find that probably the three points emphasized for the success of bone grafts explain the relative success of the foregoing methods.

Bone pegs are surrounded completely by bone and very quickly have their blood supply reestablished.

The osteoperiosteal grafts of DeLangeniere are thin strips of bone and periosteum which are laid down between the ends of the bone. If they are sufficient to maintain the shape of the limb, theoretically they are the most practical, for the blood supply is very quickly established. They offer a large surface of raw bone to stimulate osteogenesis.

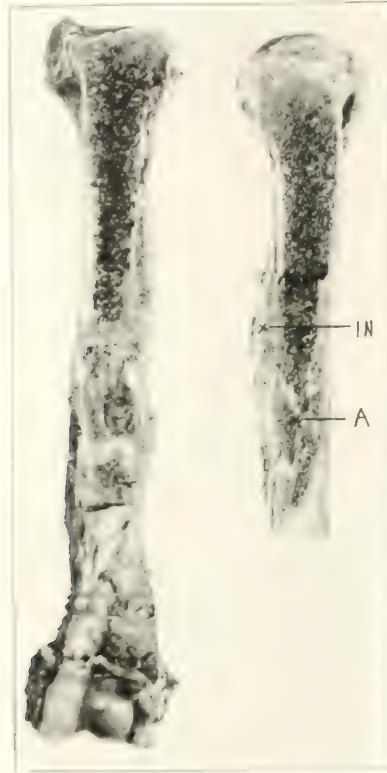


Fig. 21.—Cut-section, Jan. 24, 1920: *In*, subperiosteal bone proliferation; *A*, probable remnants of old sequestrum but no separation zone.

The inlay graft is, as a rule, rather thick and does not offer so much surface of raw bone for stimulation of osteogenesis. The late fractures that occur in these cases are probably due to the slow reestablishment of the blood supply and the resulting atrophy of the transplant.

I am inclined to believe that the intramedullary graft should be condemned. We know that the main blood supply of the shaft of the long bone is from the nutrient artery. In applying an intramedullary

graft, we destroy the blood supply of both fractured ends of the shaft and undoubtedly a longer time is required for repair on account of this to reestablish the blood supply of the graft.

In a series of experiments lasting over two or three years, I transplanted small bone fragments into a defect of from 1 to 2 inches (2.5 to 5 cm.) in the radii of dogs. Microscopic studies made at various intervals after operation showed, in the early stages, absence of the nuclei in all these grafts. There was, however, marked production

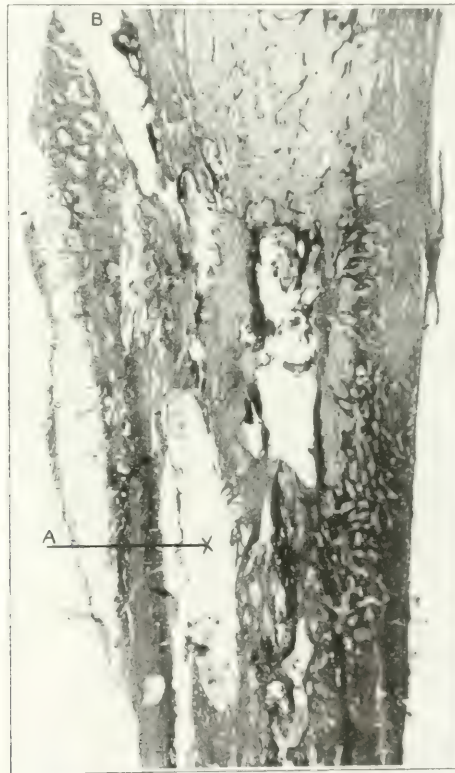


Fig. 22.—Microscopic section showing subperiosteal bone proliferation, no zone of separation: *A*, spaces in which capillary tubes lay; *B*, artefact occurring during decalcification.

of new bone about them in the granulation tissue produced immediately after operation. Firm union was the ultimate result in nearly all of these cases.

At the end of about a month, blood vessels were seen in the haversian canals of the fragments, and about each of these canals were seen two or three layers of bone cells with active nuclei. I believe that these grafts act in a manner similar to the osteoperiosteal grafts of DeLangeniére (Figs. 8 and 9).

OSTEOMYELITIS

At the present time, when radicalism is necessary in the treatment of chronic osteomyelitis in adults, I believe a word of caution should be spoken with regard to the treatment of hematogenous osteomyelitis in children.



FIG. 21 (Case 1). Roentgenogram, taken July 30, 1919; operation performed June 22, 1919, consisting of removal of 2 inches (5 cm.) of anterior surface of the upper third of the tibia: *A*, area of bone removed at primary operation; *In*, involucrum; *S*, separation zone.

The treatment of acute osteomyelitis in children may properly be divided into the treatment at the acute, and treatment at the subacute, stage. The primary indication for operation at the onset is the relief of pus under pressure, and as such, it requires the application of the

same surgical principles as pus collections elsewhere in the body, that is, adequate drainage, with the least possible trauma and with careful attention to the blood supply. If one considers that frequently periosteum with its blood supply has been stripped from the shaft by the exudation of pus and that the only remaining blood supply to the shaft is through the nutrient artery, one realizes the danger to the entire shaft of too active treatment by curettage or packing (Fig. 10).



Fig. 24 (Case 1).—Operation, June 22, 1919; roentgenogram taken Aug. 22, 1919: S, former separation zone; marked subperiosteal proliferation. No operative procedure has been performed on this area.

It is true that in the region of the metaphysis, the bony septums somewhat resemble the septums of the mastoid, and that, therefore, in this region it may be necessary to break up the compartments of the abscess. Care should be taken even here not to traumatize any more than possible.

Constant, careful postoperative observation of these cases is necessary, as there are frequent secondary metastatic abscesses in the soft parts.

Subacute Stage.—Before the days of wound sterilization, the course of a case could be fairly definitely prophesied. At the primary operation, the shaft was opened wide, frequently curetted and packed. Following this, sequestration occurred, frequently involving almost the entire shaft. As advised by Nichols, of Boston, the sequestrum was



FIG. 25 (Case 1). Operation, June 22, 1919; roentgenogram taken, Nov. 24, 1920; no sinus; patient apparently well.

usually removed at a time when the involucrum was strong enough to maintain the shape of the limb, and yet, at such a stage when the involucrum could be inverted, obliterating, as far as possible, the "dead space."

In 1919, I attempted to reproduce osteomyelitis in dogs before the students of the third-year course in regional surgery at Columbia. At the suggestion of Dr. William C. Clarke of the department of surgery, through a drill hole in the cortex of the medullary canal of the humerus,

croton oil was introduced in glass capillary tube containers having their ends sealed with agar-agar. The hole in the cortex was then plugged with bone wax, and the soft parts and the skin were sutured. By this procedure, repair following the operative trauma was allowed to progress before the croton oil was liberated from the capillary tube, probably by the solvent action of the cells and body fluids upon the agar-agar. As croton oil causes marked necrosis of the surrounding bone, we were able to produce a chemical osteomyelitis. A sequestrum,

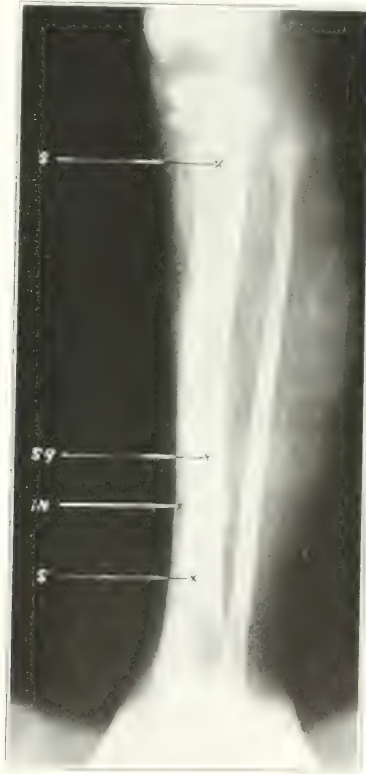


Fig. 26 (Case 2).—Roentgenogram taken, Dec. 8, 1919, previous to operation: *Sq*, sequestrum; *In*, involucrum; *S*, separation zone.

often from 5 to 10 cm. in length, and including the entire circumference of the shaft, frequently occurred (Figs. 11 to 17). This sequestrum was separated from a newly formed involucrum by a zone of debris and leukocytes; therefore, all the factors of an acute osteomyelitis were present with the exception probably of bacteria and their by-products. Sections showed the sequestrum with an involucrum surrounding it but separated from it by a zone of pus. The cortical bone of sequestrum showed absence of nuclei, and throughout its cancellous portion there

was a marked infiltration of leukocytes. The involucrum consisted of newly formed subperiosteal bone.

In the prolonged animal experiments roentgenologic studies showed the gradual disappearance of the sequestrum so that at the end of two months it was impossible to detect its former outlines by the roentgen ray (Figs. 18 to 22). Microscopic sections taken at this time showed the disappearance of the zone of separation; and the former sequestrum was then united to the living bone by blood vessels entering the



Fig. 27 (Case 2).—Roentgenogram taken, Feb. 7, 1920; operation, Dec. 9, 1919; anterior surface of the cortex of the tibia removed; drainage tube in popliteal space shown.

haversian canals. The process was similar to that found in any bone transplant, gradual absorption and deposition of new bone occurring throughout the haversian canals until all the dead bone had been replaced.

I have emphasized these facts because I believe they have a definite influence on human surgery. I shall show in the study of clinical cases that in children bone tissues that are apparently dead can be saved to advantage.

Since the introduction of the Carrel-Dakin technic, we have had results on Dr. Pool's service at the New York Hospital which correspond to a certain degree with results found in our experimental work. The following two cases show marked regeneration of bone which on either roentgen-ray or gross examination appeared necrotic.



Fig. 28 (Case 2).—Roentgenogram taken, April 10, 1920; new bone proliferation about and incorporating former dead shaft.

On account of limited time, brief summaries of only two illustrative cases will be given.

REPORT OF CASES

CASE 1 (Figs. 23, 24 and 25).—A girl, aged 5 years, came into the hospital with an acute osteomyelitis involving the upper third of the tibia. Drainage was established by removing the anterior part of the cortex in the upper

case. Later the roentgen ray revealed a marked rarefaction and apparent sequestrum formation in the lower third. As the temperature was approaching normal, and her condition was quite satisfactory, it was considered advisable to delay operation on the lower third. Later the roentgen ray revealed subperiosteal bone proliferation around this zone of separation, and a roentgenogram one year later revealed a relatively normal appearing shaft. At the present time she is well, without any sinus, and apparently the process is cured.

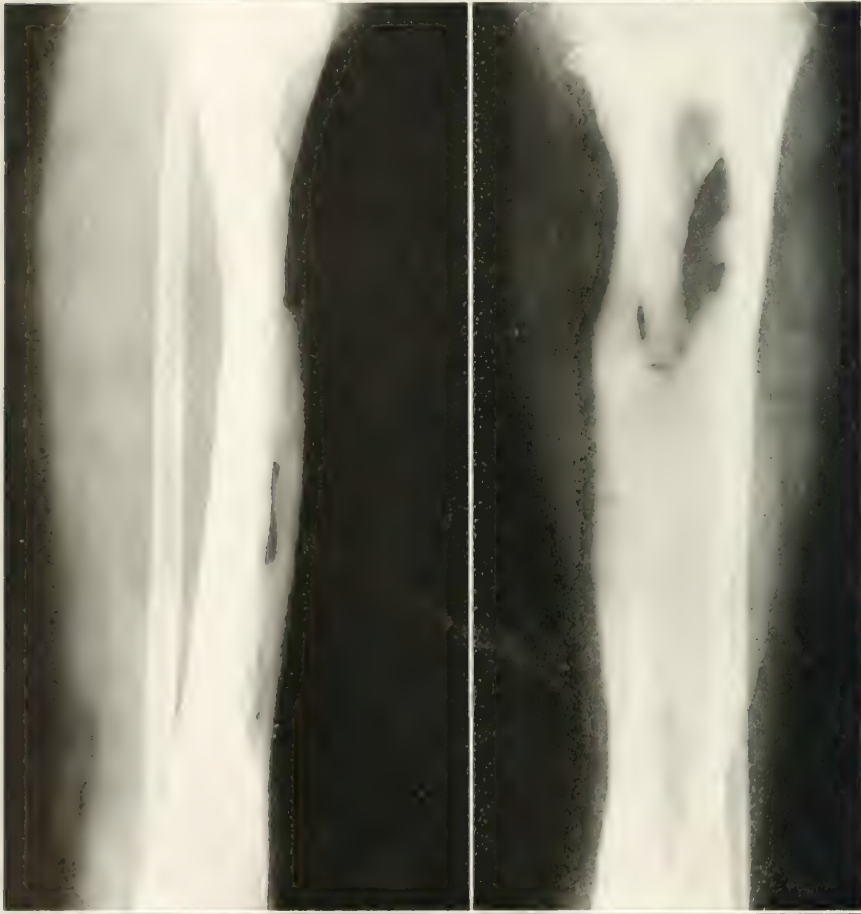


Fig. 25 (Case 2).—Roentgenogram taken, Oct. 18, 1920; new bone formation around healed patient walking on leg; feels well.

Comment.—Primary roentgenographic studies of this patient disclosed the appearance of rarefaction and sequestration in the lower third of the tibia. This completely disappeared without any operative interference.

CASE 2 (Figs. 26 to 29).—A boy, aged 7 years, in whom the tibia had been insufficiently drained, elsewhere, for an acute osteomyelitis, came into the hospital extremely ill, with a temperature of 106 F., marked leukocytosis and

prostration. At the primary operation, the entire anterior portion of the cortex of the tibia was removed. There was a fracture of the upper third due to the complete destruction of the bone. Periosteum was separated by pus from the greater part of the shaft. In this case Carrel tubes were inserted posteriorly between the necrotic shaft and the periosteum. The shaft appeared dead. It was not removed because it was thought advisable to maintain this portion of the shaft to prevent deformity. After about five weeks, granulations were seen springing up on the surface of the formerly necrotic shaft. Roentgenograms taken two months after the primary operation showed new bone formation about, and apparently incorporating, the remnant of the old necrotic shaft. At the present time, the patient has no sinus and the roentgen ray revealed marked new bone proliferation without the sign of any sequestrum.

Comment.—This patient, who was too sick to stand any operative procedure, had a dead shaft exposed in the wound. After Dakinization, granulation tissue appeared on the former necrotic surface. The bone was later incorporated and the new bone formed about it. Whether or not in this case the sequestrum was sterilized by the Dakin solution, it is difficult to state; but it appears that it acted very much as did the chemical sequestrum produced by croton oil injections in the experimental laboratory.

CONCLUSIONS

From the experience obtained with these cases and from the many animal experiments, I am convinced that, in the future in the treatment of children, we can be more conservative.

First, adequate drainage should be obtained with as little trauma as possible. Second, in cases in which the patient is clinically progressing favorably, bone, which by roentgen-ray or gross examination, appears dead, may frequently be saved to advantage in order to prevent deformity and hasten convalescence.

Finally, I believe that in the past we have made bone repair appear much too complex. We have been lost in the by-ways of periosteum, endosteum and bone reticulum. It is much simpler to believe that bone occurs as a chemical deposition in connective tissue. Such a theory allows for bone formation as it appears in all parts of the body.

In bone transplants, we must assume that the transplant per se does not live but that it acts as a framework for new bone and stimulates osteogenesis. We must, therefore, apply grafts that can easily have a blood supply established, and have sufficient free surface to stimulate bone production.

In the treatment of fractures, care must be taken to increase the blood supply. This is more important than immobilization that constricts the limb. Early motion favors union for this reason.

What we are apparently doing when a bone graft is made or when extraskeletal bone occurs in an experiment is producing the right chemical state. Then the process of bone formation inevitably follows.

Until the physical chemist tells us more of the intricacies of the chemistry of the tissues, the practical surgeon should study the circumstances of bone production, that is, what factors promote its formation. He should not let the disputes of the various experimenters over terms, or the question as to whether this or that tissue produces bone, confuse the issue. The issue requires that the patients be cured, following injury or infection of the bony structures.

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THE FATE OF NECROSED BONE IN CHRONIC OSTEOMYELITIS *

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NEW YORK

In the treatment of any acute case of osteomyelitis, the drainage of the abscess is paramount, subsequently the sequestrum and the resulting dead spaces must be considered.

In children, clinical results have shown that bone, apparently dead, may be utilized, possibly as a scaffolding for the formation of new bone, and that revascularization occurs, so that the sequestrum frequently acts in a manner similar to that of the bone graft. There is then no dead space to prevent final healing. In adults, however, we have been unable to discover any method by which this dead bone may be sterilized; and, moreover, the surrounding bone becomes so sclerosed that repair ceases. Therefore, the sequestrum in adults must be removed with subsequent closure of the dead space.

In attempting to teach the pathology and treatment of osteomyelitis to the third year class in regional surgery at Columbia University, two types of experiments on dogs were performed. First, a chemical necrosis of bone *en masse* was produced,¹ which showed the reaction of the surrounding tissues and the formation of an involucrum; second, staphylococci were injected in the medullary canal producing infected necrosis of bone.

The first type of experiment was produced by introducing, through a burr hole into the medullary canal of the humerus, a minute amount of croton oil contained in a glass capillary tube, the ends of which were sealed with agar-agar. The hole in the cortex was then plugged with bone wax, and the muscles and skin sutured. As it took some time for the croton oil to be liberated by the solvent action of body fluids and cells,

* From the Laboratories of Surgery, Columbia University.

1. Suggested by Dr. William C. Cline.

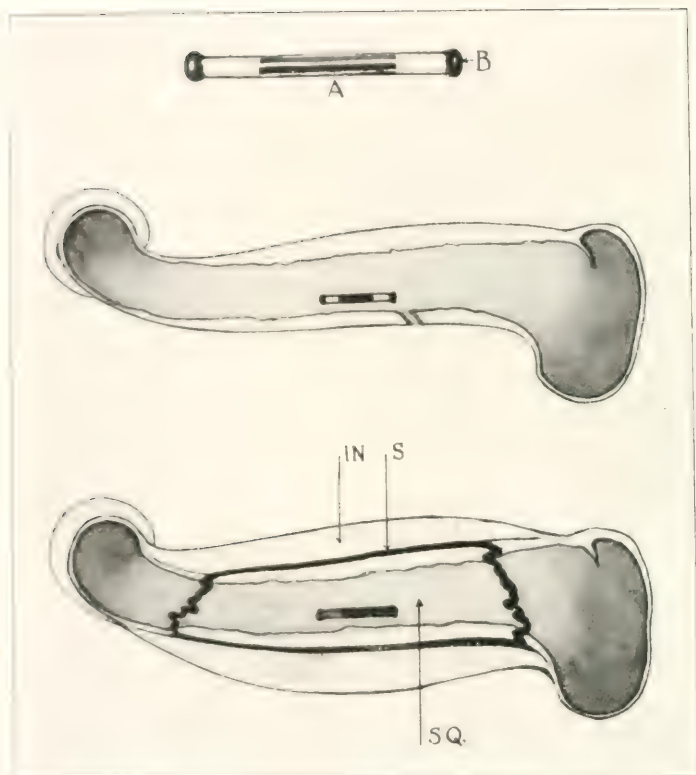


Fig. 1. Diagrammatic representation of the first type of experiment: above, capillary tube; center, insertion of capillary tube into the medullary canal through a burr hole in the cortex; below, after liberation of croton oil, showing sequestration of entire circumference of shaft: *S*, separation zone; *IN*, involucrum, and *SQ*, sequestration.

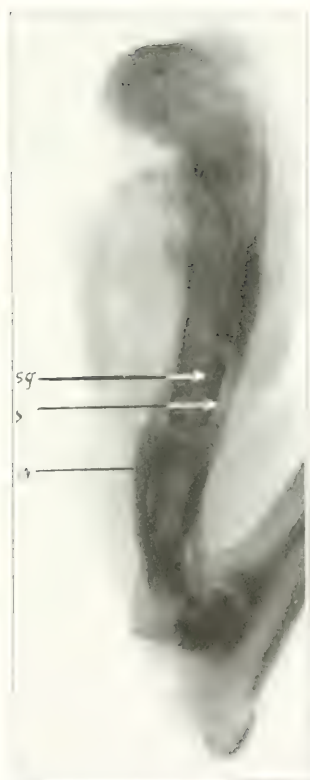


Fig. 2.—Oct. 10, 1919, capillary tube containing *Sp. 1* was inserted in the medullary canal. The animal was killed Nov. 3, 1919: *Sq.*, sequestrum; *In.*, involucrum, and *S.*, septation zone. Figures 2, 3 and 4 are of the same case.

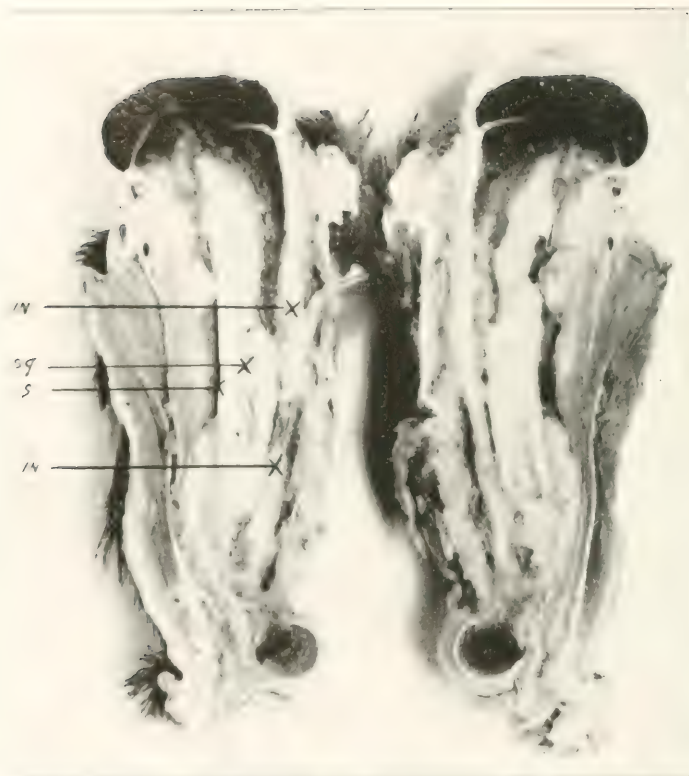


Fig. 2. Comparison showing internal structure extending almost the
 same from root. 14, squamula; 29, apical zone; 5, separation zone.



Fig. 4.—Microscopic section: In this upper part of specimen (see Fig. 1) showing during decalcification: *Sq.*, squamous; *IN*, (endothelial) *S.*, (epithelial) *IN*.

repair had taken place to a certain degree. At the end of from two to three weeks, massive sequestrums, usually of the entire circumference of the shaft and varying in length from 2 to 7 cm., occurred. Surrounding the sequestrums, as seen by the roentgen ray, was an area of separation and about this a very well developed involucrum had formed (Figs. 1 to 8).

On longitudinal section could be seen the sequestrum, appearing as dead bone, surrounded by an extensive involucrum, with a well marked area of separation. Microscopic sections showed absence of nuclei in the cancellous and cortical bone of the sequestrum, many polynuclear and mononuclear cells, in the zone of separation and through the interstices of the sequestrum, and marked subperiosteal new bone formation of the involucrum. We have here a typical picture of osteomyelitis, except that bacteria and their by-products are probably absent.

In the animals that were allowed to live, the roentgenograms showed a gradual disappearance of the outlines of the sequestrum so that at the end of about four months, it was impossible to detect its former outlines. Sections taken at this time show neither grossly nor microscopically any separation zone, and apparently revascularization of the sequestrum has taken place (Figs. 9 to 13).

In the second type of experiment, we attempted to produce osteomyelitis by inserting, through a burr hole in the humerus, a piece of gauze soaked with bouillon culture of *Staphylococcus aureus* isolated from a case of human osteomyelitis, and then transmitted through dogs and isolated from the blood stream. One of the animals in which osteomyelitis was produced lived for two months with a sinus discharging pus. He developed a cortical sequestrum which was clearly revealed by the roentgen ray. Gross section of this humerus showed a cortical sequestrum surrounded by an area of infected granulation tissue, an attempted walling off of the medullary canal by new bone proliferation, marked rarefaction of the cortex on the opposite side of the shaft, with very marked subperiosteal bone production (Figs. 19 to 21).

Microscopic sections of the rarefied cortex revealed absence of nuclei of the cortex, with new subperiosteal bone attached to this necrotic bone.



Fig. 5.—Sept. 21, 1920, capillary tube containing croton oil was inserted in medullary canal; roentgenogram taken Oct. 15, 1920, shows large sequestrum involving half of humerus: *Sq*, sequestrum; *In*, involucrum; *S*, separation zone. Figures 5, 6, and 7 are of the same bone.



Fig. 6.—Cross section showing massive s-questrum with thick involu-
crum and zone of separation: *Sq*, sequestrum; *In*, involucrum; *S*, sep-
aration zone.

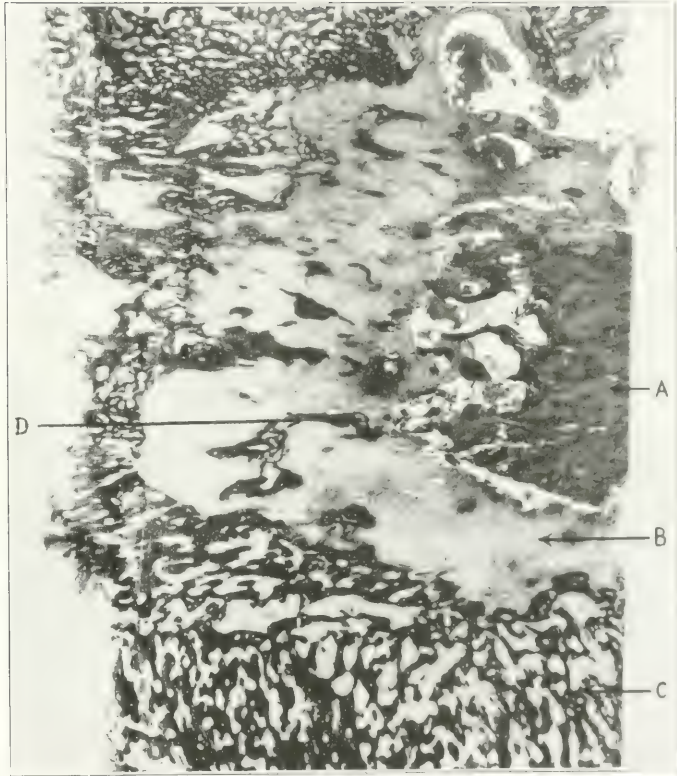


Fig. 7.—Lower power view of terminal portion of sequestrum with surrounding involucrum: *A*, sequestrum; *B*, granulation tissue; *C*, involucrum; *D*, terminal spicule of sequestrum shown under high power in Fig. 8.



Fig. 1. A. A large, dark, irregular mass (A) and a smaller, rounded mass (B) are shown. B is a small, rounded mass, sometimes and incorporating the mass.

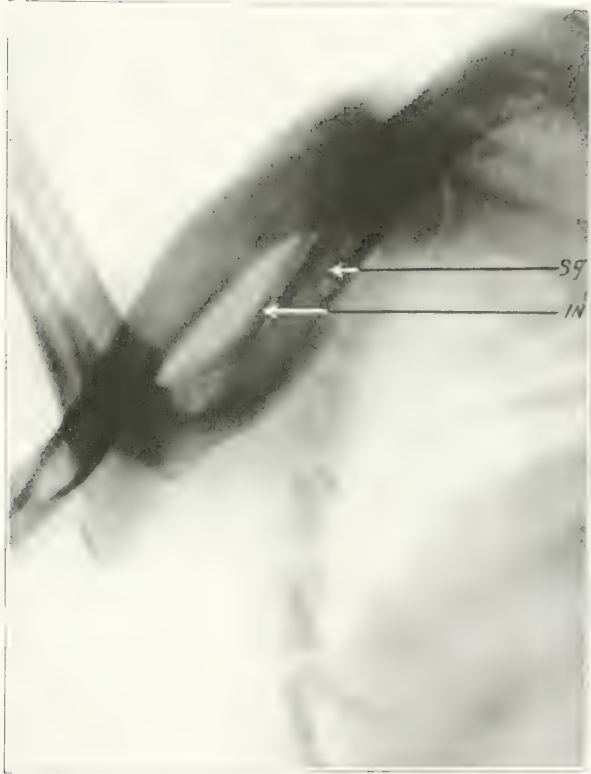


Fig. 9.—Operation, Oct. 10, 1919; roentgenogram, Nov. 10, 1919; large sequestrum with well-marked involucrum and separation zone: *In*, involucrum; *Sq*, sequestrum. (Figures 1 and 2, also of this case.)

If we take stain as a criterion of dead bone, the impossibility of detecting its cellular elements by microscopic study, then we may assume that these two types of experiment prove that dead bone frequently becomes united to living bone and persists without being isolated as an irritating foreign body. The question of revascularization of any transplant is one that demands further study.

William C. Clarke suggests the hypothesis that transplants which have relatively low metabolism may be rebuilt, molecule by molecule, through their permeation by tissue fluids and interchange of chemical compounds. We know that joint mice lying free in the synovial cavity frequently have living cartilage cells, which must be nourished by the "molecular flow" of body fluid. Clinically, there is direct evidence of revascularization of transplants, for it has frequently been observed that the graft bleeds in operations following a bone graft. Numerous observers have noted that sections of these grafts show blood vessels containing living blood cells throughout the haversian canals. No one has been able to show definitely how this revascularization occurs.

In a series of twelve cases of acute osteomyelitis in children that have been admitted to Dr. Pool's service at the New York Hospital, we have had several instances in which seemingly dead bone had become united to the surrounding involucrum and was not thrown out as a sequestrum. This conclusion was based on roentgen-ray and clinical observations. These cases have been treated by the Carrel-Dakin technic, and I believe that sterilization of the sequestrum and surrounding structures occurred. This is similar to our finding in the chemically produced osteomyelitis in our animal experiments. We, therefore, strongly advise the practice of conservatism in the treatment of acute osteomyelitis in children.

In a previous paper, I have discussed in detail the early drainage of acute osteomyelitis. It is only necessary to repeat here that care should be taken to injure as little as possible the medullary canal in the preliminary drainage. Curettage and packing of the medullary canal should be avoided as far as possible.

Ritter contends that the bone necrosis is caused by bacterial thrombosis and precedes the suppuration.



Fig. 10.—Radiograph, Dec. 3, 1911, showing bone but less marked than previously: *In*, involucrum; *Sq*, sequestrum.



Fig. 1. Schematic diagram of the connection of the pipe to the tank.

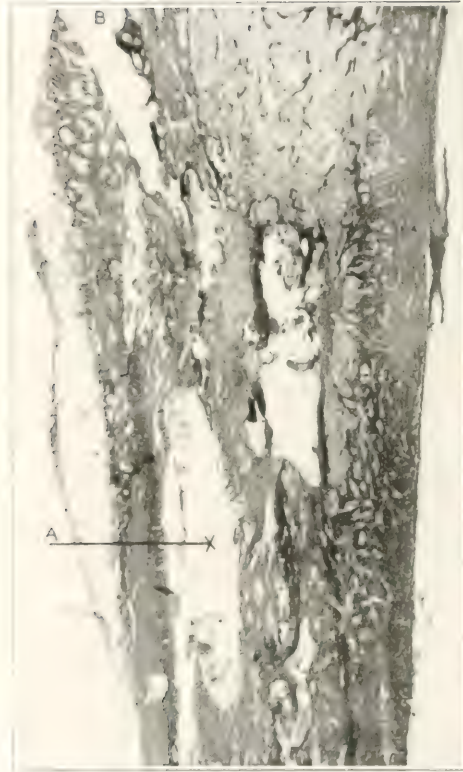


Fig. 13.—Microscopic section of specimen shown in Figure 12; subperiosteal bone proliferation; no zone of separation; *A*, space in which capillary tube lay; *B*, artefact occurring during decalcification.



Fig. 14.—Capillary tube containing sequestrum (Fig. 14, 15, 16, 17) from genogram taken January 26, showing fairly large sized sequestrum. Figures 14, 15, 16 and 17 illustrate the same.

We know that in a growing child, as long as the epiphysis persists, the diaphyseal and epiphyseal arterial systems are almost independent of each other, and that there is a relative avascular zone where sequestration usually occurs in the metaphysis.

Ritter bases his conclusion, that the necrosis is due to bacterial emboli rather than to suppuration, on the following observations: First, necrosis of the bone occurs with extraordinary rapidity in acute osteomyelitis, and not gradually, as would have to be the case if the pus were the cause of the necrosis. He believes that the bone is always necrotic no matter how early the operation is performed and that the necrosis very rarely increases following the primary operation. The bare white bone without blood vessels, stripped of its periosteum, is considered a diagnostic criterion of acute osteomyelitis. He believes that this cannot be prevented even by the earliest operation, and if a secondary operation is to be performed for the removal of the sequestrum, this sequestrum is smaller than the original area of necrosis seen at the primary operation. Second, as a rule, the necrosis is restricted to very definite localities. The total necrosis of the entire diaphysis sometimes occurs; but partial necrosis is much more common, very definite localities being attacked by the necrosis. This partial necrosis always is situated in the region of the avascular area of the metaphysis. Third, in many cases no "bone marrow phlegmon" is present. Numerous operators have observed that when the medullary canal was opened the bone marrow seemed entirely normal, not even reddened or inflamed. If his contentions are correct, bacterial emboli probably occlude these vessels, producing the early necrosis.

Numerous surgeons have observed that some cases of osteomyelitis have been cured by drainage of the subperiosteal abscess without entering the medulla.

While it seems evident that Ritter's theory is true to a certain degree, we are inclined to question him on certain of his deductions.

It is accepted that thrombosis of vessels may extend along their courses if the focus is not relieved. This is particularly true in bone in which the reaction of inflammation causes increased pressure against rigid walls. It would seem advisable, therefore, that the



Fig. 15. —Röntgenstrahlenaufnahme des 100/1000. Sequester. Durchmesser 10 mm. Größe des Sequesters und deutliche Bildung des Involucrum.



Fig. 16. *Mont. C. longipennis*, further diminished in size and with a well marked separation zone.



Fig. 17.—*A*, normal limb as controlled; *B*, almost complete disappearance of sequestrum as shown by the roentgen ray.



Fig. 16.—Osteomyelitis is a disease caused by the injection of *Staphylococcus aureus* into the medullary cavity (Sq., surgical incision). Marked new bone production resulting in wall off medullary canal, and compensatory subperiosteal bone proliferation on the opposite side. Figures 18, 19, 20 and 21 are the same bone.



Fig. 19.—Cross-section of bone. *Sg*, sinus; *C*, cartilage; *B*, bone; *C*, periosteal bone proliferation.

earliest relief of this pressure should be accomplished by exploratory operation and drainage. If pressure is not relieved, it is logical to assume that the thrombosis of the entire nutrient artery, with the consequent death of the diaphysis, might ensue. After studying his theory, I believe we may agree to the following factors in osteomyelitis: First, that early drainage should be performed to relieve tension and to limit as far as possible the primary thrombosis; second, that when roentgenograms reveal circulatory disturbance of bone due to thrombosis, there may be a later reestablishment of blood supply and the affected bone may become revitalized.

REPORT OF CASES

Our present interest is, however, the treatment of the late necrosed bone, a condition that frequently occurs in children following the preliminary drainage. The cases reported here show that bone which appears dead either on roentgen-ray or gross examination may be utilized to the advantage of the patient.

CASE 1.—A girl, aged 5 years, came into the hospital with an acute osteomyelitis involving the upper third of the tibia. Drainage was established by removing the anterior part of the cortex in the upper third. Later the roentgen ray revealed a marked rarefaction and apparent sequestrum formation in the lower third. As her temperature was approaching normal and her condition quite satisfactory, it was considered advisable to delay operation on the lower third. Later roentgenograms revealed subperiosteal bone proliferation around this zone of separation, and a roentgenogram taken one year later disclosed a relatively normal appearing shaft. At the present time, she is well, without any sinus, and apparently the process is cured.

Comment.—Primary roentgenographic studies of this patient demonstrated the appearance of rarefaction and sequestration in the lower third of the tibia. This completely disappeared without any operative interference (Figs. 22 to 24).

CASE 2.—A boy, aged 7 years, whose tibia had been insufficiently drained elsewhere for an acute osteomyelitis, came into the hospital extremely ill, with a temperature of 106 F., marked leukocytosis and prostration. At the primary operation, the entire anterior portion of the cortex of the tibia was removed. There was a fracture of the upper third, owing to the complete destruction of the bone. Periosteum was separated by pus from the greater part of the shaft. In this case, Carrel tubes were inserted posteriorly, between the

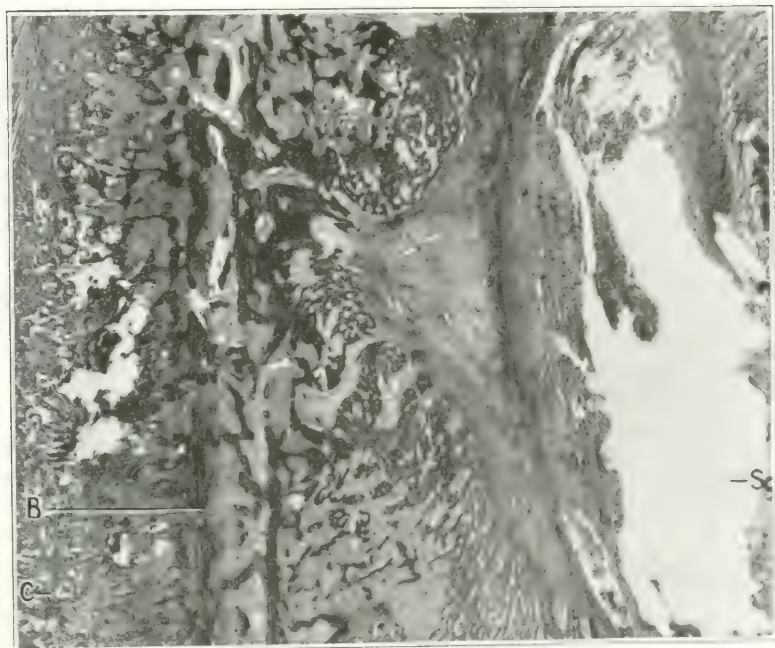


Fig. 20.—Low-power photomicrograph of the cavity of a bone cyst. The granulation tissue with new bone production at the margins of the cavity is surrounded by areas of leukocytes and pyknotic granulation tissue.



Fig. 1. Organizational structure of cortical bone of bone along in Fibrous bone. *A* - living bone, consisting of the presence of an osteon; *B* - transitional bone, that is the intermediate state, the bone would be with absence of bone nuclei; *C* - living subperiosteal bone.

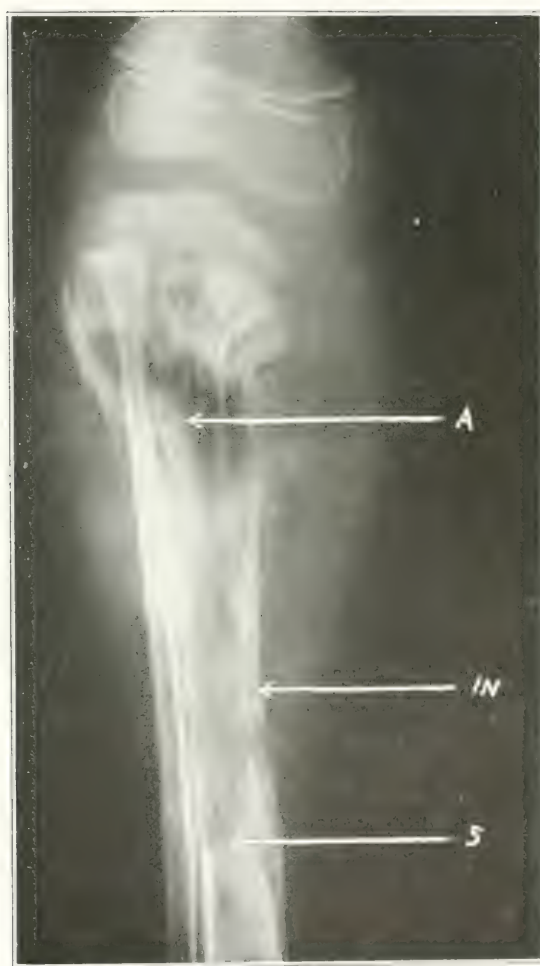


Fig. 32 (Case 1).—Reconstructive Allis-Johnson operation performed June 22, consisting of removal of the anterior surface of the upper third of the tibia: *A*, area of bone removed at primary operation; *In*, involucrum; *S*, separation zone.



Fig. 23 (Case 1).—Operation, June 22, 1919; roentgenogram taken August 22: *S*, former sep-



Fig. 24

Fig. 24 (Case 1).—Operation, June 22, 1919; roentgenogram taken November 24; no sinus; patient apparently well.

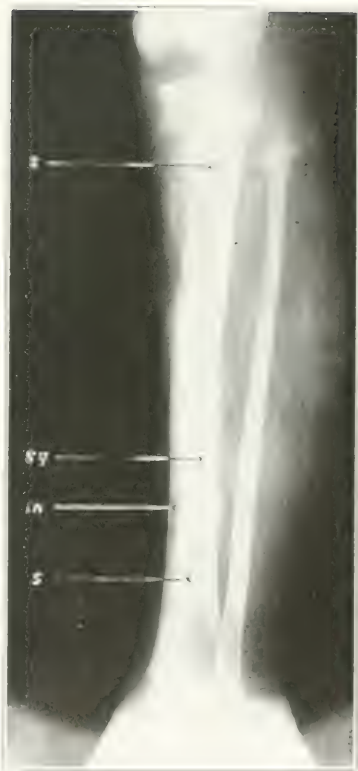


Fig. 25

Fig. 25 (Case 2).—Roentgenogram taken Dec. 8, 1919, previous to operation: *Sq.*, sequestrum; *In*, involucrum; *S*, separation zone.

necrotic shaft and the sequestrum. The shaft appeared dead. It was not removed because it was thought advisable to maintain this portion of the shaft to prevent deformity. From 1916 until 1920 *Streptococcus hemolyticus* blood infection and was treated with intravenous injections of peptone. After about five weeks, granulations were seen springing up on the surface of the formerly necrotic shaft. Roentgenograms taken two months after the primary operation demonstrated new bone formation about, and apparently incorporating, the remnant of the old necrotic shaft. After two years, the child was well without a sinus (Figs. 25 to 27).

Comment.—This patient, who was too sick to stand any operative procedure, had a dead shaft exposed in the wound. Following treatment by the Carrel-Dakin method, granulation tissue appeared on the former necrotic surface. The bone was later incorporated and the new bone formed about it. Whether or not in this case the sequestrum was sterilized by the surgical solution of chlorinated soda (Carrel-Dakin solution) it is difficult to state; but it appears as if it were acting very much as did the chemical sequestrum produced by croton oil injections in the experimental laboratory.

CASE 3.—History.—A boy, aged 10 years, admitted in September, 1920, had been suffering from stiffness and throbbing pain in the left knee for four days. While playing baseball, four days previously, he struck his left knee against a stone, which was being used as a base—"was sliding to the base." The next day the knee began to swell slightly and to throb. He was unable to put his foot to the floor without pain in the region of the knee joint. He became unable to bend the knee without intense pain. His condition became progressively worse until the time of his admission to the hospital.

Examination.—The temperature was 104 F.; the pulse, 120; respiration, 24. The white blood count was 22,100, with 87 per cent. polymorphonuclears. The patient lay in bed, with the leg rotated outward and with flexion of the knee of about 30 degrees. He complained of pain on motion of the knee. There was marked tenderness about the knee and lower end of the femur. The maximum point of tenderness was on the inner side, in the region of the internal condyle of the femur, and, posteriorly, in the popliteal fossa. Deep and continuous pressure over the femur higher up caused excruciating pain. There were several large and tender inguinal nodes. There was a small elliptic abrasion over the internal malleolus of the tibia.

The diagnosis of osteomyelitis of the metaphysis of the femur was made, on account of the history and the fact that, while there was fluid in the joint, the main tenderness was in the region of the lower epiphysis of the femur. The roentgen ray revealed a slight fuzziness, posteriorly, in the region



Fig. 26 (Case 2).—Roentgenogram taken Feb. 7, 1920; operation, December 9; anterior surface of the cortex of the tibia removed; drainage tube in popliteal space. (Courtesy, Dr. J. H. H. H. H.)



Fig. 14 (Plate 27). *Proteromys* (taken May 3, 1932); top up and
side well, as done, complete reproduction of tibial shaft.



Fig. 38. Case 3.—Acute osteomyelitis of femur. A. Active area of ossification in posterior portion of metaphysis.



Fig. 30. Same as Fig. 29, showing latent virus. Same July 3, 1959, showing latent infection and subepidermal tissue proliferation. Operative SEM (left) and SEM (right). The tissue is beginning to proliferate.



Fig. 30 (Case 3). Roentgenogram taken May 28, 1922, (third view), without any swabs and almost complete disappearance of the sequestrum.

Operation and result.—A long incision of the lateral surface of the femur was made. The periosteum in the lower third of the femur was stripped from the bone. It contained about 2 ounces (50 c.c.) of pus. On palpation, the bone felt roughened externally. On account of the extreme prostration of the patient, it was thought advisable to explore the medullary canal. Two burr holes were, therefore, made along the supracondylar ridge. From the lower one, bloody serum with some broken down fat escaped under tension. As the abscess cavity pointed toward the popliteal space, it was thought advisable to drain in that region. A small longitudinal incision was made and a tube inserted. Carrel tubes were inserted in the lateral wound. There was some swelling of the knee joint for a considerable time, but this gradually subsided without treatment. The wound was treated by the Carrel-Dakin method.

The boy left the hospital on the forty-fourth day. The roentgenograms at that time disclosed considerable proliferation about the lower end of the femur and suggested a possible sequestrum. However, from my experience in previous cases, I believe that frequently bone that appears necrotic in the roentgenogram will, in children, become reorganized, and that if the child is progressing well clinically, it is favorable to wait for a considerable period of time (Figs. 28 to 31).

Nov. 17, 1921, the wound was completely healed. The child ran and played without pain. Examination revealed a linear scar, no bone tenderness or induration and no limitation of motion of the knee joint.

CASE 4.—History.—A baby girl, aged 17 months, three days before admission, had become fretful and feverish. Her parents took her to a physician, who immediately referred her to a hospital.

Examination.—The baby appeared acutely ill, with a temperature of 104.2 F.; pulse, 120, and respiration, 36. The white blood count was 20,000 with 91 per cent. polymorphonuclears.

Operation.—An incision was made over the entire length of the left thigh. There was marked edema of the muscles; but in cutting through the deep fascia, a large abscess cavity was opened, which completely surrounded the femur and was largely extraperiosteal. The periosteum was scraped back over the lateral surface of the lower third of the femur. With a drill, a small hole was made, about 4 inches (10 cm.) above the lower end. Pus escaped from the medullary cavity. A similar opening was made 1 inch (2.5 cm.) distad from which pus also escaped. With a gouge, the medullary canal was opened between these two holes and a considerable amount of broken down tissue was removed from the canal without curetting. A counter stab wound was made on the



Fig. 31

Fig. 31 (Case 3).—Roentgenogram taken May 25, 1941, showing no sequestration, no sinus, no limitation of motion, nor bone tenderness.

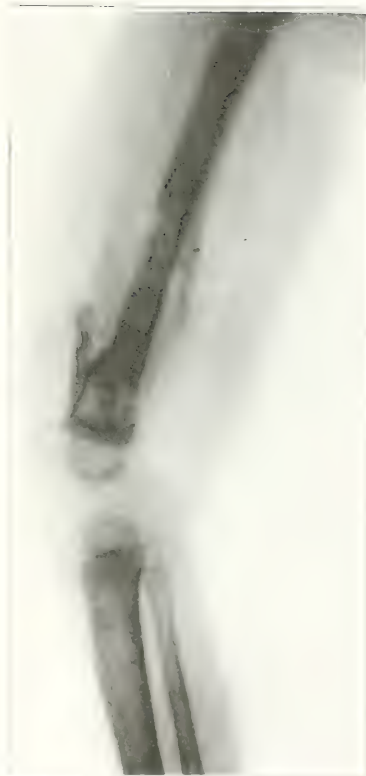


Fig. 32 (Case 4).—Roentgenogram taken July 7, 1941, showing no sinus, no limitation of motion, no interference and considerable subperiosteal bone proliferation.



Fig. 32

Fig. 32 Case 41—July 27, 1931, marked subperiosteal bone proliferation; appearance some what suggests chronicity; suggest further investigation.



Fig. 33

Fig. 33 Case 41—Sept. 16, 1931—marked subperiosteal bone production; no signs of osteomyelitis; growing secondary arthritis.

mesial surface, below the extensor tendon. Carrel tubes and Dakin gauze were inserted along the side of the femur, but none were placed in the medullary canal.

Culture revealed a pure growth of *Staphylococcus aureus*.

Result.—The child was discharged from the hospital on the sixty-fourth day, with a normal temperature. The incision was completely healed; but there was a small sinus from the mesial stab wound.

Three months after discharge, forceps were inserted and a small cortical sequestrum removed. As can be seen by the intervening roentgenograms there has been marked reaction and new bone production. I am convinced that if in this case the femur had been opened wide and packed, an entire sequestrum of the shaft would have occurred (Figs. 32 to 34).

The wound has now closed completely and the child is well.

CONCLUSIONS

1. If necrosis of bone is frequently a circulatory disturbance and not of necessity suppurative, we may assume that a bone appearing necrotic under the roentgen ray may become revascularized. The process then is similar to that occurring in a bone transplant.

2. Bone which to gross examination appears dead, lying in an infected field, may occasionally be rendered sterile and utilized as a framework for the production of new bone about it. Under these conditions, if the clinical course of the child is progressing favorably, we should hesitate to remove the bone which, either on roentgen-ray or gross examination, appears necrotic, if it can be saved to advantage. It frequently happens that the involucrum is not strong enough to maintain the shape of the limb, and therefore, deformity may be prevented, and operative procedure, which is always accompanied by a certain degree of shock, may be avoided.

100 East Sixty-Sixth Street.

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EXPERIMENTAL RECONSTRUCTION OF THE OESOPHAGUS BY GRANULATION TUBES

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VARIED attempts by widely different operative procedures have been made to solve the problem of reconstruction of the oesophagus after removal of segments of the organ. It has been realized for a long time that this is a basic problem in the surgery of oesophageal stenosis, for, whether the lesion is a benign or a carcinomatous stricture of the organ, the ideal would evidently be a restitution of the passage for food after operative removal or side-tracking of parts of the organ. The many experimental and occasional clinical efforts that have been made with this purpose in view have consisted either in partial or in total oesophagoplasty. It would lead too far afield to enter into the details of these methods. In brief, it may be said that the earliest plan was the formation of a skin tube fashioned from the skin of the anterior chest wall, to which the oesophagus above the stricture was attached superiorly, and the stomach below. Later developments consisted in the use of implants of loops of small or large intestine isolated in various ways, and, finally, tubes or flaps from the gastric wall were employed for this purpose.

Experimentally, these methods have been followed by occasional successes, and there are a few instances in which clinically, too, they have proved satisfactory. In the human being such procedures involve multiple operations over a period of many weeks or months, with the ever present likelihood of failure from complications, infection or gangrene of the isolated portion of the hollow viscus, etc. The technique of these oesophagoplasties is complicated, and the patient must necessarily be in good physical condition to withstand the several major operations. In fact, against

the few successes that have been reported, there is the probability of a much larger proportion of unreported failures and an operative mortality that is not negligible.

If progress is to be made in this field it is essential, we believe, to separate the problem of oesophagoplasty into two distinct parts -- a plan of operation adaptable for benign stenosis and one for cancer of the oesophagus. In the former, a considerable length of the organ may be involved or the strictures may be multiple; the patient is usually young and in good physical condition, and the problem is one of sidetracking and not of removing the disease. In cancer of the oesophagus the patient is ordinarily old and debilitated by the disease; and the problem is one of replacement of relatively short segments of the organ. It is the latter problem that has engaged our attention in the experimental studies.

Before describing the experiments, brief reference should be made to the methods employed for re-establishment of the food channel in the two successful cases of its resection for cancer. In Torek's case no attempt at reconstruction was made. A rubber tube connected the stump of the oesophagus in the neck with a gastrostomy opening. Lilienthal employed a pedicled skin flap laid in place at the first operation, which consisted in the isolation of the neoplasm. After the removal of the growth, the skin flap was detached and the final result was a dermal channel to which the oesophageal ends became attached. The patient was a young individual in good physical condition; it is questionable if the procedure employed by Lilienthal will prove applicable to the cases of oesophageal cancer that are usually encountered. Indeed, it was from observations made during the

from the brilliant series of operations were carried out in his case that we were led to perform our experimental work.

Repair of a wound of the œsophagus takes place by granulation tissue. Even a simple œsophagotomy with immediate suture will be followed by leakage until the incision in the organ is healed by granulation. An erroneous impression exists that anastomosis between the œsophagus and some other hollow viscus will be followed by repair as seen in the peritoneal cavity. The œsophagus has no serosal covering and the repair after operations upon the abdominal hollow organs depends primarily upon the existence of the serosal layer. Since repair of the œsophagus takes place by granulation, we determined to make use of this fact by establishing granulation tubes between the œsophagus stumps after resection of the organ. Our plan was to isolate a given section of the œsophagus and surround it by packings. At the next stage the isolated portion was to be resected and a rubber tube sutured in place. It was our impression that granulations would form about the tube and that the œsophageal epithelium would ultimately line the granulation tube.

The experiments comprise a series of operations performed on thirteen dogs, all under ether anaesthesia. The first operations were on the thoracic œsophagus. Attempts were made to approach the organ through the posterior mediastinum, but the pleura was invariably entered and death ensued from infection. The principles involved being the same and the technical difficulties fewer, operations on the cervical œsophagus were practiced in all the subsequent experiments. A striking fact was soon noted in these experiments on the cervical œsophagus: resection and rubber tube implantation in one stage was followed by death from infection. A suppurative process extended from the wound down the cellular planes of the neck into the mediastinum to involve both pleural cavities. The following experiment will illustrate this:

Experiment 1. Dog 1775. Weight 27 pounds. Operation, February 4, 1921. Incision 4 inches, along anterior border of left sternomastoid muscle. Three inches of œsophagus were isolated from

trachea and surrounding muscles, after retraction mesially of the great vessels and vagus nerve. One inch of œsophagus was resected, and a T-tube inserted and sutured into cut ends. The sternomastoid muscle, with a small arm of T-tube coming through it, was sutured, thus completing a muscular tunnel around the tube. The skin and fascia were closed. A typical Witzel gastrostomy was done.

February 5, 1921. Dog died. At autopsy the wound in the neck was found extensively infected, with pus bathing the muscles, trachea, and cut ends of the œsophagus; these ends, however, were held by the sutures to the tube. The infection extended down the cellular spaces of the neck into the posterior mediastinum, a purulent exudate covering the œsophagus, trachea, and prevertebral muscles. In addition there was a bilateral bronchopneumonia with a bilateral empyema, apparently a direct extension from the posterior mediastinum. Death was due to an overwhelming infection and sepsis.

On the other hand there have been no deaths from infection in the operation carried out in two stages, and we, therefore, regard this as the correct procedure. The technique is in brief as follows: A vertical incision is made to the left of the trachea and the œsophagus is exposed by retraction of the musculature and great vessels. The vagi are stripped free, the branches going into the segment to be resected being sacrificed. The desired portion of the œsophagus being thoroughly isolated, gauze packings are placed beneath it, the ends coming out of the wound. The latter is left wide open. At the second stage, one week later, the isolated portion of the œsophagus is elevated by traction on the packings and is divided obliquely above and below. The packings and the segment of œsophagus are then removed. A bed of granulation tissue is found to have formed beneath the packings. A soft rubber tube of the diameter of the œsophagus is securely sutured to the upper and lower ends of the organ by stitches passed transversely. The rubber tube has a lateral opening in order to feed the animal by a catheter passed through it into the stomach. When the tube becomes loose it is removed if it has not already been discharged from the wound.

By this time the external wound is largely closed by granulation tissue. An œsophageal fistula, or rather a fistula through the new formed granulation tube, persists but finally closes completely.



Fig. 1. End of first stage of operation. Œsophagus isolated from surrounding structures and packed off. In the actual operation, packings completely separate the organ from the trachea, great vessels, and muscles.

Three experiments illustrate the process of gradual reconstruction of the œsophagus by the granulation tube operation and their description indicates the results that have been obtained.

At the end of one week the ends of the resected œsophagus are partly attached to a gutter of granulation tissue. Upon microscopic examination there is beginning union between the cut ends of the œsophagus and the adjacent, partly formed granulation tube, the first stage of epithelial overgrowth extending from the œsophageal epithelium.

Experiment 2. Dog 1965. Weight 11 kilograms. *Operation, first stage, April 1, 1921.* An incision was made to the left of the trachea, from the lower margin of the sternomastoid muscle, upward along its anterior border, to the lower pole of the thyroid gland. The sternomastoid was retracted laterally; vessels identified, isolated and retracted. The œsophagus was found behind and a little to the left of the trachea. The left vagus nerve was carefully freed and retracted with the vessels, those branches to the œsophagus being sacrificed over the portion to be isolated. Two and one-half inches of œsophagus were isolated, surrounded by wet packings, and the wound left wide open. April 1 to April 8, dog was given normal diet by mouth.

Second stage, April 8. Weight, 10.5 kilograms. Granulations were red and healthy. The œsophagus was drawn out of the wound by means of the packings, and the packings were removed. The upper limit of the isolated area was cut across obliquely, with

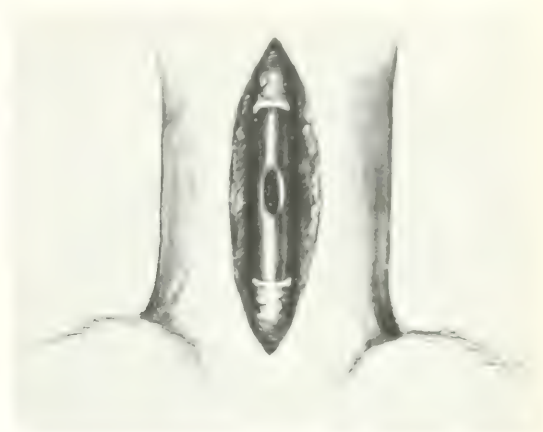


Fig. 2. End of second stage of operation. A portion of the œsophagus has been resected and replaced by a rubber tube, sewed into place above and below. The tube bridging the gap lies on a bed of granulation tissue.

the dorsal wall of the organ longer than the ventral. A soft rubber tube was inserted into the upper cut end, and the edges of the œsophagus sutured to it, taking four sutures, one behind, one in front, and two laterally. These sutures were passed transversely, and the knots were tied on the outside. With the upper junction of tube and cut œsophagus now secure, the œsophagus was cut across below and the lower end of the tube sutured here in a similar manner. About 2 inches of the œsophagus were removed. A window was cut into the tube for feeding purposes. The wound was left wide open.

April 11. Dog has pulled tube out. Œsophageal ends found and another tube inserted and sutured in place. Feedings through an opening in it are to be continued.

April 13. Tube has become loose again; left out. The lower end of the resected œsophagus can be seen glued down firmly to the surrounding granulation tissue. The upper end is not yet attached. Feedings to take place through the œsophageal fistula, through which a catheter can easily be passed into œsophagus, thence into the stomach.

April 15. Since yesterday the animal has been vomiting and breathing with difficulty. Death.

Autopsy. Infection of wound is limited to site of operation. The lower cut end is firmly glued down to the granulation tissue, and it appears that the posterior wall of the granulation tube which has replaced the œsophageal defect is lined with epithelium; its color is light pink and has a glistening appearance, resembling the normal œsophageal mucosa. The upper cut end is not yet glued down to the granulation tissue around it.

Death was due to operation which was performed during pregnancy.

Microscopic sections. Sections taken through the junction of the œsophageal cut ends and the granula-

Two tubes were an abrupt ending at the oesophageal wall as indicated on the surface by a dipping down and a heaping up of the epithelium. At this site there is a termination of the mucous glands and the muscularis ends by intertwining with the adjacent tissue. This latter is granulation tissue presenting the earlier stages of organization, with here and there islands and groups of polynuclear cells. Toward the free surface, vascularization is more marked; there are many new-formed blood vessels. The surface is covered in part by an extension of epithelium continuous with the oesophageal epithelium. This new-formed epithelium, however, presents the following differences from normal oesophageal epithelium: (1) there are no papillae; (2) it is not as thick; (3) it stains more deeply; (4) flattened surface cells of normal oesophageal mucous membrane are not present; (5) nuclei of cells are round throughout; (6) very active mitoses are present; (7) there is some polynuclear infiltration.

Three weeks after operation the granulation tube is solidly formed, with some distortion because the external fistula through the same still persists. The union between the divided ends of the oesophagus and the granulation tube is firm, and there is a more extensive epithelial overgrowth arising from the oesophageal epithelium.

Experiment 1. Dog 1300. Operation, not done. February 11, 1921. Typical Witzel gastrostomy done through a left upper rectus incision. Five centimeters of cervical oesophagus were isolated by the usual technique, as already described. Packings were placed around the oesophagus and wound left wide open.

February 11-18. A tube has been inserted into the gastrostomy opening for feedings only. Six ounces of milk were given twice a day and 7 ounces of water four times a day; moderate emaciation; animal in satisfactory condition except for diarrhoea.

Second stage, February 18. Resection of 3 centimeters of oesophagus completed with insertion of tube in usual manner.

February 23. Tube has disappeared from wound; apparently in the stomach.

February 25. Condition of dog is satisfactory. Oesophageal fistula, about 2 centimeters long, is present. It seems that the defect has been bridged by granulation tissue. Dog to be given water by mouth.

March 1. Gastrostomy permitted to close. Rubber tube in stomach, as shown by X-ray picture.

March 10. For the past 2 weeks the dog has been taking fluids by mouth. Most of it passes into the stomach, about 5 per cent escaping through the fistula in the neck. However, in a few minutes after swallowing food, it is regurgitated and escapes either through the fistula or is vomited.

Autopsy, March 11. There is no infection of the wound. Oesophageal defect is occupied by a thin, pinkish white tube of tissue, loosely attached to the surrounding musculature and the trachea. There is gradual merging of normal oesophageal wall into the tissue occupying the defect. The interior appears to be lined by a smooth layer continuous with the oesophageal lining. The new-formed tube, showing no stenosis, is about 4 centimeters long and of about the same diameter as the oesophagus.

Microscopic section. The termination of the oesophagus is indicated on the surface by a slight dipping in of the epithelium; it is only marked definitely by the ending of the mucous glands in the depths. The musculature grades into the tissue that occupies the defect, well beyond the termination of the mucous glands, thinning out gradually, and becoming ultimately intertwined with the young fibrous tissue. The new-formed epithelium is similar in appearance to the old, being of about the same thickness. Papillae are now well developed, the staining appearance is almost identical with that of the normal, and there is developed a subepithelial layer of tissue similar to the submucosa of the oesophagus, with very little leucocytic infiltration.

For the rest, the tissue occupying the defect is of about the same thickness as the oesophageal wall, and presents granulation tissue with considerable organization and many new-formed blood vessels. Sections from the upper and lower junction of the oesophagus with the new-formed tube, when taken together, present the evidence that there has been considerable growth of epithelium over the granulation tube. The middle portion, however, remains uncovered by epithelium and presents heaped-up masses of polynuclear cells on the free surface of the granulation tissue.

A dog kept for 7 months after oesophageal reconstruction by a granulation tube was in satisfactory physical condition during that period. After an early stage of disturbed deglutition accompanied by repeated regurgitation of food, this animal was able to swallow fluids and mush, but no large fragments of food. A stenosis of the oesophagus at the site of the granulation tube was noted, and it was apparent that this could have been dilated by bougies. However, dilatation was not practiced because we wished to learn if the stenosis would be progressive, and thus vitiate the operative procedure. The stenosis remained stationary and was found at autopsy to have resulted in the reduction of the normal circumference by about one-fourth. Furthermore, the autopsy showed that the oesophageal ends had been drawn toward each other, reducing

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the original defect of 5 centimeters by about one-half. The lining by overgrowing epithelium was complete and the new-formed "oesophageal tube" was of the same thickness and of greater resistance to hydrostatic pressure than the adjacent oesophageal wall.

Experiment 4. Dog 1020. Weight, 15 kilograms. Operation, first stage, March 18, 1921. Isolation of 7 centimeters of cervical oesophagus by usual technique.

Second stage, March 25. Resection of 5 centimeters of oesophagus. The tube was sutured in place in usual manner.

April 1. Weight, 14 kilograms. Animal in good condition; has been taking feedings of milk and glucose water well. Does not regurgitate.

April 8. Three days ago the tube became loose and slipped into the stomach. The oesophagus was probed but the tube could not be felt. An exploratory laparotomy did not reveal the tube in the stomach or intestines; evidently it has been passed per rectum.

April 15. Weight, 12 kilograms. For the past few days the dog has been vomiting his milk. The milk is kept down for a short time and is then regurgitated. Soup and finely divided pieces of meat were tried with no better result. The dog swallows the meat, but it is caught in an oesophageal dilatation, due probably to a lack of nervous innervation. In a few minutes the meat and soup are vomited, some coming through the fistula, but most of the mixture coming out of the mouth. After repeated swallowings and acts of vomiting, the food remains in the stomach. Holding the animal up on his hind legs does not seem to aid in keeping the food down. Feedings through the fistula are to be discontinued; dog is to get meat, soup, milk and glucose water by mouth only.

April 22. Weight, 10.75 kilograms. Dog is in fair condition, although he still regurgitates food. A No. 20 bougie, when passed, meets an obstruction at the region of the fistula and passes it readily.

May 11. The general condition of the dog is good. He is very active, and runs around normally. Fluids are kept down better. *Oesophagoscopy* by Doctor Yankauer shows a stenosis at the site of the new-formed tube.

May 27. Weight, 10.75 kilograms. The fistula is closed. A No. 20 bougie meets an obstruction at this region but passes it easily. The stricture is apparently being gradually dilated by the passage of food.

October 17. Weight, 9.5 kilograms. During the summer the condition of the dog has been good. Regurgitation of food has gradually become less, although it still occurs.

Chloroformed.

Autopsy. In the region of the operation, thin fibrous tissue loosely binds the oesophagus to the surrounding structures. There is considerable

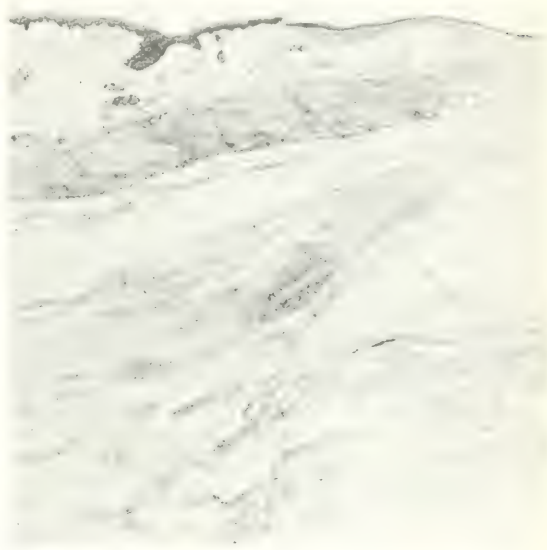


Fig. 3. Junction of normal oesophagus and replacement tissue at the end of one week. Low power (10x) showing abrupt ending of normal epithelium indicated by heaping of cells. The newly formed epithelium begins at this point.

dilatation of the oesophagus above the reconstructed tube; the latter is narrowed by about one-fourth the lumen of the normal oesophagus. The new-formed portion is 4 to 5 centimeters in the fresh state as represented by whitish tissue different in color from the normal pinkish oesophagus. It is of the same thickness as the normal oesophagus, and when viewed from the inside a smooth, glistening lining completely covers the surface, bridging the area from normal oesophagus above to normal oesophagus below. Very fine blood vessels may be seen coursing from normal mucosa to the regenerated mucosa.

With the specimen removed, active peristaltic waves starting from the dilated portion proceed across the reconstructed tube to normal oesophagus below; active retroperistalsis passes in similar fashion. At times it seems as if the peristaltic wave skips the new-formed tissue; at other times a definite contraction through it is observed. This peristaltic action lasted for over an hour, in the isolated specimen, without immersing it in any physiological fluid medium.

Microscopic. Sections taken through the area of reconstruction show, on the surface, epithelium which has regenerated completely, there being no tissue left uncovered by epithelium. The new epithelium is similar to normal epithelium with perhaps the slight difference of more highly developed papillae. The defect is occupied by fine-meshed fibrous tissue, which toward the surface resembles submucosa, and in the depths is a connective tissue rich in blood vessels. The tissue comprising the defect is as thick as normal oesophagus above and below.

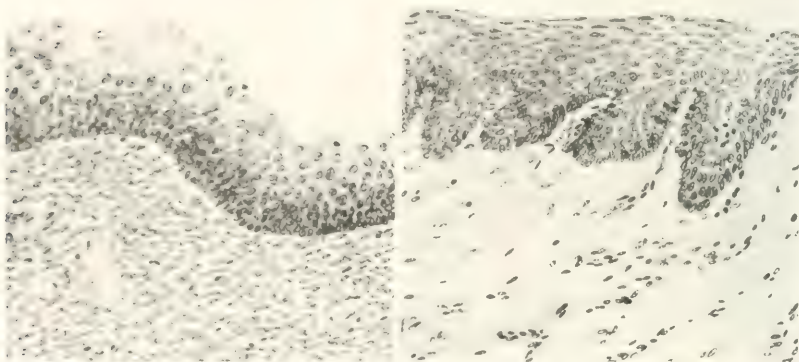
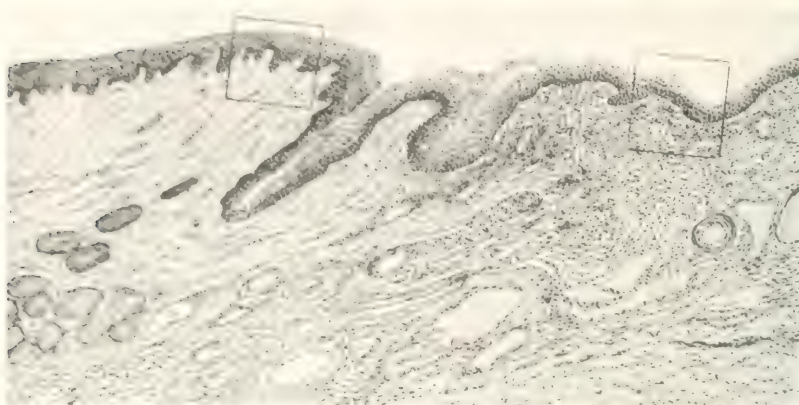


Fig. 4 (above). Medium power drawing of junction at the end of one week, showing ending of mucous glands and the differences between the normal and newly formed epithelium.

Fig. 5 (below, left). High power drawing of normal oesophageal epithelium at site of first square above.

Fig. 6 (below, right). High power drawing of newly formed epithelium at site of second square. There are no papillae, no flattened cells at surface. The nuclei are round throughout, active mitosis and leucocytic infiltration in submucosa.

As far as the actual reconstruction of the oesophagus by a granulation tube is concerned, we believe the difficulty would not be as great in the human being as in the animal experiments. In the latter there was always the problem of controlling the animal and of retaining the implanted tube for the desired period. It proved impossible to prevent the swallowing of all sorts of septic material even in the presence of a gastrostomy; dressings could not be kept in place, etc. The technique, as we believe it to be applicable to the human being, may be described as follows: Following gastrostomy, the first stage of the operation would be the exposure

of the cancer of the thoracic oesophagus through the posterior mediastinum by the extrapleural approach as described by Lilienthal. An operable condition being found, the portion of the oesophagus bearing the tumor is isolated from surrounding structures, including the vagi, the branches entering the neoplasm being sacrificed. The isolated segment is surrounded by a sling of rubber dam on the outside of which packings are placed. The wound is left open in large part or completely. Superficial packings are changed when necessary, but deep packings are left undisturbed unless there is evidence of infection in the wound. It may be mentioned

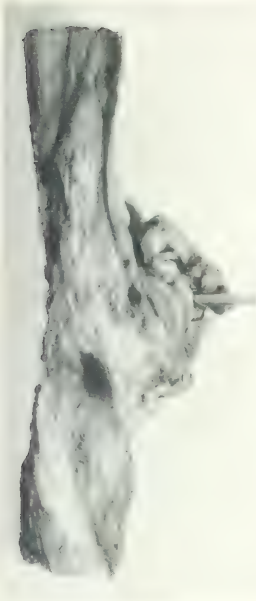


Fig. 7.



Fig. 8.



Fig. 9.

Fig. 7. Granulation tube occupying defect. Three weeks after operation. Newly formed tube is of a lighter color than normal oesophagus. Stylet indicates fistula leading into neck.

Fig. 8. Same as Figure 7, opened up, showing granulation tissue bridging gap between normal oesophagus above and below.

Fig. 9. Photomicrograph of junction of normal oesophagus and newly formed tissue, three weeks after operation. Section indicates ending of mucous glands. Musculature intertwines with the newly formed fibrous tissue. Regenerated epithelium very similar to the normal, with well developed papillae.

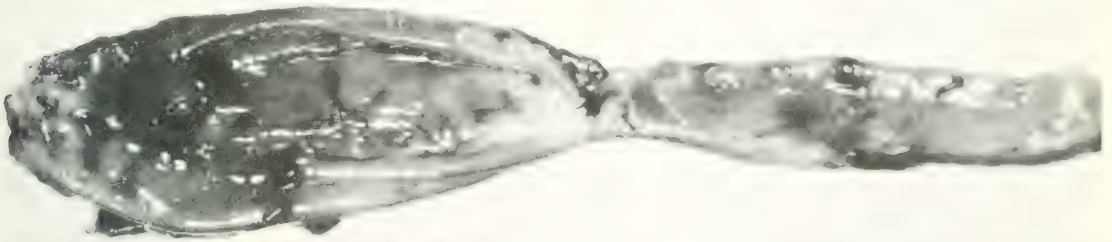


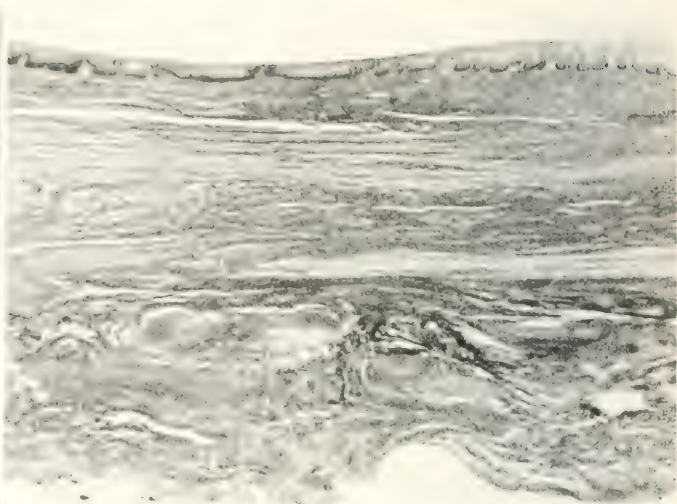
Fig. 10 (above). Specimen of oesophagus and newly formed tube 7 months after operation. Stricture narrowing lumen by one-fourth normal diameter is shown, with dilatation above.

Fig. 11. Same specimen filled with water, bringing out in greatest size of stricture which corresponds to that of the former oesophageal fistula.



FIGURE 11. Specimen opened up. Contraction of musculature; reconstructed area different in color from that of adjacent esophageal wall.

FIGURE 12. Cholangiogram, showing the reconstructed area, contrasting with normal biliaryium. The newly



formed epithelium is similar to normal epithelium. Junction point is indicated by ending and intertwining of muscle bundles. The thickness of the newly formed esophageal wall is the same as that of the adjacent esophagus.

In passing that mediastinal suppuration can be present without clinical evidence, for in a case in the experience of one of us (H. N.) in which the above described first stage operation was done, a walled-off collection of pus in the mediastinum was unexpectedly encountered at the second stage operation performed one week after the isolation of a cancer of the thoracic esophagus. At the second stage operation, the section of the esophagus would be drawn toward the surface of the wound by traction on the rubber dam. The esophagus would be divided above and below the neoplasm, not straight across but obliquely with the idea of reducing stenosis of the divided ends. A soft rubber tube would be chosen with a diameter of the filled esophagus. One end of a long strand of silk would be fastened to the tube, the other end being brought out of the mouth and strapped to the cheek. The rubber tube would extend about 4 centimeters up and down into the esophageal ends, and fixed to the wall of the esophagus by sutures of chromic gut passed transversely to esophageal axis, with knots tied on the outside. Packings would be loosely placed about the

rubber tube and the wound would either be partly sutured or left wide open.

This technique of rubber tube implantation would appear to be applicable only to esophageal resection below the level of the arch of the aorta, and would probably have to be modified for tumors opposite or directly above the arch. In a patient operated upon by one of us (H. N.) in whom the neoplasm lay directly above the arch, the tumor-bearing portion of the esophagus was isolated and the esophagus stripped free up to the root of the neck. It was then divided below the neoplasm and a rubber tube sutured in place. The wound was packed with gauze and left open. The patient died of hemorrhage from an intercostal artery 9 days after the first stage operation. It was planned at the second stage to expose the esophagus in the neck, draw the tumor-bearing portion into the cervical wound, divide the esophagus above the growth here, draw rubber tube into neck and suture it to the upper esophageal stump.

Clinical experience will, of course, be necessary to determine if results similar to those noted in the animal experiments can be obtained, and whether a one- or two-stage

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operation will be required. From our studies, however, we believe it justifiable to advocate the reconstruction of short oesophageal defects such as those encountered in resection for cancer, by the granulation tube method we have devised.

SUMMARY

A simple experimental method has been devised in which a granulation tube is employed for the reconstruction of the oesophagus after its resection.

Fatal mediastinal infection follows its attempt in one stage.

The two-stage operation is successful. In the first stage the section of oesophagus to be removed is isolated and in the second stage it is resected and a rubber tube is implanted.

A granulation tube forms with epithelial overgrowth from the oesophageal ends beginning in one week and becoming extensive at the end of 3 weeks.

The longest period of observation was 7 months after operation. In this case the new-formed tube was well developed and completely lined by oesophageal epithelium. A partial stenosis appeared soon after operation but was not progressive.

The method is advocated as applicable for reconstruction of the oesophagus after resection for cancer.

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ANALYSIS OF METHODS OF MODERN MEDICAL EDUCATION *

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NEW YORK

The dilemma which confronts us today in any consideration of medical education is two horned. On the one hand we have the vast and ever-increasing fund of information that must be given to the student, and on the other, the shortness of the allotted time in which to give it to him. Methods of teaching must be found that are best suited to the majority of students, and that will serve to prepare them for the practice of medicine or for a life of research. What should be taught must also be decided. The good and the bad in past and present medical education must be remembered in order to solve this problem. Present methods have failed to deal adequately with the difficulties of the situation, and, if they are persisted in, the purposes of the medical school will be increasingly defeated.

The day of the morphologic ultramechanical impress on medicine, inculcated by the continuous study of dead tissues, has passed. The life-giving conceptions which the study of physical chemistry has given to all chemistry must be developed in advancing medicine. Medicine must thus vitalize its anatomy, its physiology and its pathology.

The medical schools as never before must develop the scientific spirit in research and in their teaching. The scientific spirit is that which influences a man to seek evidence and to seek it whole heartedly and dispassionately, whether it proves him right or wrong. No effort in science is wasted except the insincere effort. No medical school can reach the heights in education and continue on such a plane without this development in its ideals.

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IMPORTANCE OF "PREMEDICAL" EDUCATION

In this consideration of medical education, no analysis has been made of the most important and difficult problem of "premedical"¹ education partly because it is impossible to do it justice and treat it as a subheading of the topic under consideration. Ideally, the student should learn of the relationship of the fundamentals of knowledge at as early an age as possible. His understanding of the interrelations of philosophy, ethics, biology and physical chemistry should be so thoroughly cultivated as to become of the nature of an essence, not a veneer. And this knowledge of the sciences must rest on a foundation of history and of the classics. Such students would solve many of the problems of medical education and make a suitable complement for able instructors.

The reorganization of medical education may be considered under five main subjects: (1) teachers; (2) students; (3) the subject matter included in a medical course; (4) methods of teaching and of study, and (5) the chief aims in medical education and the present hindrances to their attainment.

TEACHERS

A teacher is one who interests students in learning so that they endeavor to acquire knowledge for its intrinsic value. The fundamental difficulty lies with the teachers themselves. Boas² says: "Intelligence does not come from the acquisition of facts; intelligence is insensitive to a mere fact; it reacts only to ideas. . . . The issue is the education, not of the student, but of the teacher."

Good teachers must not only be intelligent: they must understand and sympathize with the student's outlook, be able to keep alive the student's interests. A good teacher feels that he learns from his own students through an intimate association with their ideas. It is only through a constant revaluation of his own methods in the light of student opinion and by comparison with his colleagues that he can hope to grow.

1. "Premedical" courses are given in many colleges. They attempt to give physics, chemistry and biology to remedy the dogma of authority which has hindered understanding. Until the teachers of primary schools supplement their own efforts, an introductory medical course should supplement earlier education by attempting to develop the students' minds in seeking the truth.

2. Boas, George: What Do Teachers Know? Atlantic Monthly, May, 1918.

Who, indeed, can teach ably year after year, isolated from all ideas and criticism except his own?

The effect on the students of the personality and attainments of able men is well recognized. Their undefinable influence may be profoundly felt throughout an entire school; it may be as inspiring and dynamic as that of a Pasteur. Until schools make every effort to select for teachers men of stimulative personality, most teaching institutions will continue to be crowded with "good hearted," acquiescent individuals.

Continuance of Poor Teachers.—Much blame must be laid at the door of those who appoint the inferior teachers. Possibly their appointment may be excused, but the policy common to so many medical schools, of allowing them to remain year after year, cannot be forgiven.

Student Advice.—One of the main reasons for the continuance of poor teachers and poor methods in the medical schools is that student opinion is looked down on. The bitterest criticism by students at once changes into the most helpful advice as soon as they realize that they are listened to without prejudice and with sympathy. In a successful business, because success is dependent on output, complaints and advice of consumers are never ignored. Dickenson Miller has pointed out that "each professor knows only his own classroom, and the dean knows all the professors but not all their classrooms, while the students alone have a survey over the entire curriculum and see all the classrooms."

"Student advice" does not in any way refer to the partisan, back-stairs gossip of student cliques, telling the teacher only what they think he wishes to hear. By student advice is meant the general student opinion of the methods of the individual teachers, who hold their interest, who aid them to think, and under whom they gain related knowledge.

When the private quiz system was in vogue, some quiz masters continued to teach year after year, for they were the ones from whom the students learned. The mediocre and poor teachers discontinued their quiz within a few years. With roll-calls and compulsory attendance at college quizzes, this effective and silent criticism has been lost, and the teacher who is not teaching has found a sinecure in those medical schools in which the student's spoken opinion is not regarded.

In universities in which the courses are all electives, the useless teacher is automatically eliminated. The docent system in vogue in German universities recognizes the value of student opinion to such an extent that the man who desires to teach after he has qualified as a docent is simply given a room to teach in. If the students come to hear him and take his courses, he is considered a successful teacher, and it is from the successful docents that the professors are chosen.

THE STUDENTS

Professor N. B. Pillsbury has drawn our attention to the fact that "one of the chief functions of education is selection." Education does not make stupid people intelligent, it merely aids in selecting the intelligent and develops their potentialities.

Though the average ability of the students entering a medical school remains about the same year after year, there are striking mental and physical differences among these "selected" men. Their perceptive power varies greatly; some learn best by their eyes, a few by their ears. No two of them have the same affective response to any situation. This response differs greatly even in a single individual from day to day. A good teacher is aware of these potentialities in individual students. He makes use of as many "affects" as possible to teach, to stimulate and interest them. He finds those most nearly attuned to his own emotional response the ones most helped by his personality.

The students' early education—their surroundings, whether sons of doctor, lawyer, soldier or sailor, have all produced an effect. A way must be found to help those who have not had previous opportunities to acquire something of the outlook which comes from a scientific and an intelligently critical atmosphere. If the school hopes to raise its standard, some system of selecting those desirable must be employed other than using high school and college "marks." In fact, if possible, the aptness of students for medicine and their general honesty of purpose should be determined before they are accepted. Methods which inspect the students—those about to enter and those already enrolled—from every angle, mental, moral and physical, will help in selecting the best to practice medicine.

SUBJECTS TO BE TAUGHT

Too much is forced into the schedule today. That there should be an extensive reduction in the number of required hours will readily be granted; but the manner in which this should be done is still undecided. The long standing lack of sympathy between the pure scientist and the pure clinician, each seeking to over-emphasize one side of medicine, is a difficult complication.

The brunt of this lack of sympathy has fallen on the student, and it is for him that the two must be brought together. Medicine must make all developments of pure science eventually of practical use. The pure scientists must be asked for the answers to the problems of life. Therefore, for a medical school to do the most for its students, these links in knowledge must be continually fitted into the chain of education. The students who wish to go into pure science are entitled to every opportunity in the medical school. At the same time, the community has every right to expect that medical schools shall always provide the best for those who are to become practitioners of medicine.

It is evident that subjects of great importance to modern medicine have as yet found no place in our curriculum. There is a continuous up and down in the estimated value of methods of diagnosis and of therapeutics. Scientific knowledge concerning the relation of mental to bodily disease, and the methods of understanding and dealing with the resulting complexities, have been ignored almost to exclusion in many departments. Psychology has too intimate a relation to the science of healing to permit a first class medical school to exclude it.

In many schools, biology has been approached purely structurally. The angle worm and the frog have been dissected. The ameba and the paramecium have been drawn. It has not effectively developed the basic conceptions of life and its interrelatedness. The tissues have been treated as if dead; or, if alive, separated from the dynoplasm³ of the animal. Biology should tell of the interrelation of the living cell with its environment, of heredity and of the energetics of living tissues, and act as a direct introduction to bacteriology, to

3. Dynoplasm: a term to suggest the inseparability of the many manifestations of the living tissues; the inseparability of physicochemical actions and of substances. H. A. Moore.

histology, otolaryngology, and particularly to medicine and surgery.

In any schedule flaws and omissions can be found. Yet "teaching in" so many subjects has led to much of the superficial study of the present day. The thing to be learned is how to evaluate knowledge. Such evaluation can best be reached by concentration and by correlated study in all their ramifications of a few subjects which best lend themselves to provide a background of medical knowledge.

Elective courses through which the students may fit themselves more fully for one or another phase of medical work play at present practically no part in many curriculums, so that only through the required courses does either pure scientist or clinician meet the students.

METHODS OF TEACHING AND OF STUDY

The greatest faults are those of commission; too much is being taught, and the material taught is unco-ordinated. The different methods by which students have been prepared to become fit to practice medicine may be condensed into four general groups:

Group 1, in which the student attends passively, is constantly guided, dependent on the experience of others; A, the lecture; B, assigned textbook study; C, laboratory demonstration and clinical presentation of cases.

Group 2, in which the student both listens and talks: the quiz, conference and discussion.

Group 3, in which the student observes, reports and discusses: experiments and cases in the dissecting room, laboratory and clinic.

Group 4, in which the student takes the entire responsibility: student experimentation and investigation, either in the laboratory or in the study of cases in hospital or dispensary.

GROUP 1.—In which the student attends passively, is constantly guided, dependent on the experience of others. A. *Lecture System*.—Under this method of teaching, the relation between student and teacher is at its thinnest. The teacher cannot really know what effect his words are having on the students individually. Some lecturers almost expect the students to take stenographic reports of their lectures, and many attempt to do so, swallowing undigested the material flung out to them. The mental strain of madly

writing down what they hear hour after hour, and of attempting to think at the same time, is bitterly fatiguing. If the lecturer is good, there is a constant sense of disturbance due to the fact that there is no outlet for the stimulus he creates. To those who do not take notes, the lecture, as one professor of biology remarked, "is a method by which the student is enabled to lean back perfectly at leisure and observe the personal peculiarities of the lecturer. Moreover, it is a kind of a sedative, an opiate to all parties, by which in the presence of a thin substitute for education, they are able to forget the aching need of the reality." In lectures, as one college professor has put it, "the ears do most of the work, using only one of the senses. In order to fix a subject in a student's mind, he must experience the things talked about."

Aside from these real faults of the method, it is the one almost invariably used by the poorest teachers. The students speak of most lecturers as purveying cut and dried or "canned" knowledge, in that they follow some favorite or personally written textbook. The lecturer often uses the same notes year after year, unaware of their weaknesses. This could not happen so often if the students could be persuaded to ask questions during the hour, or could remember what to ask about at the end, and if there were real opportunity to do so. But questions are rarely asked, and the lecturer rarely comprehends his audience; he unconsciously presents blocks of knowledge, the relationship of which is not evident to the student. Small gaps or defects in the presentation of a subject are stimulating to the student who attempts to fill them in by mental effort and thus is led to think and to reason. But if the breaks are too great or too numerous, no amount of mental effort will make the student able to keep up with the train of thought, and he will eventually cease to supply the gaps between the bits of new information and the familiar knowledge given.

A plea for the lecture system is that much time is saved for a busy man, who may talk to a large class; but this is a poor argument in the eyes of the students, unless the lecturer gives more than can be found in a textbook. The lecture, however, is a simple and valuable means of leading the student safely through a new and difficult process of thought. A good lecturer

can do this better than any book, and at far less expenditure of time and waste of effort on the part of the student; but he must be an unusual teacher, one who can think more rapidly than his students, and who can feel intensely whether or not the latter are following his argument. He must state conflicting ideas without prejudice, and explain the process of reasoning by which he has arrived at his own opinions. The man who comes fresh from his personal activities, whether from the clinic or the laboratory, and talks vividly of his work, gives much more than mere facts, in that he instils enthusiasm. The value of such a man as a teacher and inspirer can scarcely be overestimated. His stimulation leaves the student in a sensitized frame of mind.

Good lectures, if few and scattered, are useful, but good lecturers are rare. Further, if many good lectures were used, their composite effect would still be fatiguing; collectively, they would defeat just what makes any single lecture a success.

The fact that there is frequently no textbook arrangement which fits the curriculum of a school makes it impossible to abolish the lecture system completely, without loss of its correlating tendency.

Whatever the value of a single lecture, a long series of scheduled lectures in a day is educationally unsound. The students say that by the third hour they have fallen into a sort of daze, and that by 5 o'clock they are mentally paralyzed, utterly unfitted for the evening's work.

B. Textbooks.—These are invaluable, if several opinions on subjects are made available and if the student is fully aware that usually each book represents merely the opinion of one man. Too often assigned reading is from those books alone which agree with a teacher's opinion. Students frequently complain that if they do not recite according to the assigned text, their statements are held as wrong even though they follow other authority. The teacher who assigns so many pages per lesson and asks in recitation for an unassimilated return of the material, lays his qualifications as a teacher open to serious doubts. Unfortunately, such use of books tends to fix even more firmly in students' minds the fallacy that the printed word must be true.

Even books that record only those observations which the writer regards as facts must not be thought of as authoritative. If the student reads opposed statements, made in all honesty by two or more "authorities," the experience is convincing that all books must be handled with mental care and read without prejudice.

C. Laboratory Demonstration and Clinical Presentation of Cases.—These should be distinguished from laboratory and clinical work, in which the specimens, cases and experiments are handled directly by the students. A series of specimens or cases is lectured on and exhibited; the students are passive listeners, and even those in the front rows can see but little, rarely anything that they are not told to see. Here, again the students' powers of critical observation of the facts presented are but little developed.

The method may have some uses, however; for instance, in the presentation of some difficult experiment, the technic of which requires so much time or is so difficult that the student is incapable of doing it himself; or in the exhibition of some exceedingly rare and seldom seen clinical case, such as anthrax or leprosy. Quite aside from what the student may learn of the clinical case presented is the inspiration which he will often acquire from watching an instructor who is an adept in the art of extracting all the essential facts about a patient, while at the same time gaining his complete confidence.

GROUP 2, in which the student both listens and talks. —*The quiz conference and discussion.* These may be regrouped either under an autocratically dogmatic procedure or a Socratic procedure. The dogmatic method suits many teachers, since they can more readily follow one textbook, and pleases some students, who then receive blocks of knowledge as facts which can be readily pigeon-holed in mind and note book, to be turned in at examination time. With the Socratic method, the teacher is under more of a strain; he must be mentally alive, continually matching his wits against the students'. By their example, teachers in this way help the students to think and to weigh evidence, and thus to build up for themselves coordinated knowledge.

The dogmatic procedure does not train the student to think; it teaches him only to remember. The objections to it are practically the same as the objections to the didactic, dogmatic lecture already discussed.

The Socratic method, in which the teacher and the students, by questions and answers, proceed from one bit of knowledge to another, because there are definite connecting links, can be used only by teachers thoroughly familiar with their own and interrelated subjects. The students are continually oriented as they proceed. This method forces the teacher to be aware of the students' mental equipment and progress.

In the quiz and conference, the student need not sit passively awaiting his turn, and, having recited, sink into a safe and sleepy neutrality; he can take a large part in the constructive work—how great a part is dependent especially on the ability of the teacher, but also on the development of the student.

The essence of merit in the quiz conference method is that coordination of subjects can be assured. This coordination in knowledge tends to develop an awareness of what is important or unimportant in each subject. Thus, the student's burden is trimmed with discrimination as he proceeds.

GROUP 3, in which the student observes, reports and discusses specimens, experiments and cases with which he has come into direct contact in the laboratory and clinic.—By this method, the students are forced not only to think, but also to see for themselves. That they are desperately in need of such development is evident each time we hear them say, "I do not know what I am expected to see," or, on the other hand, when they see or hear what they are told to, even if it is not present: they can always feel a spleen.

The good teacher who understands the possibilities in coordination of topics usually also appreciates the differences in students' powers of observation and mental development. Under the method of individual study, he has opportunity to lead each, step by step, to observe and to understand what he sees. If students are first shown complicated specimens or cases, they become confused and acquire less knowledge than when they begin with simpler ones. Their studies must always be related with one another and with bits of knowledge already possessed. The success of this method for many students is dependent on the ability of the teachers, since the present day premedical development has not been such as to make students able to stand on their own feet.

On the other hand, this method is intensely stimulating to those well equipped, able to observe and learn without constant help. It is also an important aid in the selection of the most desirable students. The students who memorize facts and do well through their accuracy in presenting them, who are able to graduate at the top of their class through marks thus received, do not always shine when acquiring knowledge by personal observation and when they are forced to think for themselves. This is no criticism of any student with a good memory: only of those whose memories alone commend them. Such students are not of the type who advance general knowledge or who make good physicians; they should be recognized and taught to think, not encouraged by good marks to a false sense of their superiority. Individual observation forces each man to use his own senses, not accepting the evidence of another; reporting such observations requires of him an accuracy that he is willing to defend; interpreting them requires of him judgment and use of bits of knowledge previously acquired; and discussing them gives him an opportunity to defend his position and become aware of the degree of validity of his judgments.

GROUP 4, in which the student takes the entire responsibility: student experimentation and investigation.—*Independent study*. This is comparable to the "honors" system prevalent in English universities, wherein the student is free to study in his own way and is himself the judge of the time when he feels fitted to present himself for his examinations. Aside from the general basic knowledge required to pursue the course he has chosen, he is free to follow up the subjects that interest him most; always with the help and guidance of a tutor, who, though he is usually an instructor or research worker in one branch of science, must have his knowledge so well correlated that he will be able to guide the student in all branches. Examinations under this system come, not as a lock to close forever any part of the student's mind deemed by the professor to be sufficiently crammed, but as a key to give the student a further understanding of the relationship between the masses of knowledge he has accumulated throughout the years.

The method of independent study may not be practical for the average medical student of today, but is it not worth while to give to the better men a special chance to develop, even if they are an extremely small minority? Since this method tends to develop the resourcefulness of the capable student, it at least can be combined in many ways with a didactic scheme. With sufficient free time granted in the schedule, a student may study and experiment for himself under the heads of any of the main laboratory courses. Paternalism does not tend toward individual development: there is failure to throw the student on his own resources in not forcing him to think. A method which permits students to work independently and does not so carefully guard them that errors may not occur in experiments and observations tends to force each student to formulate his own conclusions. Thus, in spite of much poor teaching, the intelligent students will educate themselves, learning to weigh evidence and, through experience, acquire judgment.

DEVELOPMENT OF THE STUDENT

What is it that a school through all these methods of teaching seeks to develop in the student? Whether he is to become a pure scientist or a practitioner, in order to accomplish most for himself and others, must he not, as a student, acquire a truly scientific habit of mind? He will then in practice make use of available knowledge without prejudice. From the aspect of pure science, the value of this attitude is generally acknowledged; but from the standpoint of the community, this attitude for the clinician is even more important. For is it not through the practitioner that practical application is made of the discoveries in science? In fact, is it not probable that much of the lack of sympathy between the laboratory worker and the clinician has been engendered by the failure of the clinician so often to make full application of science in his practice and by the failure of the laboratory worker to develop a truly scientific spirit in future practitioners while they are students?

INCULCATION OF SCHOLARSHIP

The inculcation of a high degree of scholarship and an insistent craving for knowledge as something ideal is also most desirable. If those who have been taught at

the College of Physicians and Surgeons, New York, in the dissecting room at any period during the last thirty years, will analyze that experience, they will see that Dr. George S. Huntington's impress on them to do well with honesty of purpose was of much more value than the knowledge of anatomy they acquired.

ENCYCLOPEDIA TEACHING

Have not medical schools fallen into the error of feeling that they must pack into the students' minds great masses of facts, more or less useless, but which must be found in that encyclopedia of medical information, the completely educated student? Why attempt the impossible? Must he not "practice" medicine during the rest of his life before his education can be completed? If the teacher of long ago realized this when he adopted the word "practice," how can it be hoped that all knowledge of medicine can be imparted at the present time in four years?

Should not medical education rather aim to have students able to judge what is important and what is unimportant, or at least to give them an opportunity to undergo experience and to practice their judgment? They are then better qualified to be on the lookout for evidence, and to evaluate it as they find it. No teacher can lay down rules for discovering the important or unimportant, while the general teachers of anatomy, of bacteriology, of chemistry, of histology and of pathology must treat all fields as of equal importance.

Until there is a close coordination of the needs of many specialists, unimportant details will still seem to the student to be of equal value with the most important.

RELATEDNESS

Should not medical education particularly aim to link for the future practitioner of medicine all specialties so that their relatedness may be ever before him? Students are lost in the maze of seemingly contradictory statements of specialists. What the gynecologist teaches seems to contradict the teachings of the urologist, and the obstetrician disagrees with both, simply because each does not know of the needs of the other. Cooperation and interdepartmental sympathy with the necessities of specialists would not only save time in the study of medicine, but would give the students this much

perfect interlinking of the parts to form an orderly whole.

Relatedness is essential for comparison, and it is on comparisons that knowledge is built. It is necessary that topics and subjects be overlapped. Therefore, no topic can ever be regarded as finished: the practice of medicine is continuous and so is its study.

NONMEDICAL HEADS OF DEPARTMENTS

For the sake of such relatedness, the heads of all departments must be intimately acquainted with the needs of medicine. Medical experience alone can give this acquaintance. In choosing heads of departments, the search again is for men preeminently interested in the education of the medical student, and it is the exception for a man without a medical degree to have had such experience that his perspective will enable him to see his own subject in a coordinated relation with medicine as a whole.

DEPARTMENTAL BARRIERS

Interdepartmental partitions which are the inheritance of tradition and custom are distinct barriers to coordination. The terms physiology, pathology, medicine and surgery suggest that they are subjects apart, while in reality physiology and pathology shade by insensible gradients into each other and again into medicine and surgery. All of these rigid departmental partitions are imaginary. The present custom of departmental education in medicine tends to separate teachers both by a physical living apart, and by mental discord, because of different tenets and purposes. When the old line subjects—*anatomy, physiology and pathology*—were taught by a single practitioner, the students did not suffer from such discord.

THE BLOCK SYSTEM

From time to time, courses have been altered by the introduction of the so-called block system, whereby subjects are attached and finished in rotation. This is bad for two reasons: 1. What is learned by study of only a few minutes a day, carried through the years, results in the acquirement of more actual knowledge than that acquired by a continuous application over a short period of time. 2. The block system is not

adapted to the material which is taught. It treats knowledge as if it could be divided into bricks, each one to be finished and packed away, a box when filled with such bricks to constitute a medical education. Knowledge of a topic, on the contrary, is no such solid matter, but is interdependent and vanishes if not kept alive through its increment. This block method obviously defeats all aims at correlation and orientation of students.

Students who are "fed facts" because they are "not capable of discrimination," as undergraduates, are not trained to judge wisely and with discrimination when they enter on their independent medical lives. Physiology can never be acquired to the full by assigning 800 hours of a schedule in the first year "to get it out of the way," as one man put it. Rather to be fully assimilated must physiologic thought and physiologic investigations continue throughout the four years, interwoven with medicine and surgery. Must not the "fundamental scientific subjects" be carried into the later years? Thus the student will be able to pick with more readiness the essentials from the nonessentials in his pure science courses. To be able to do this to the full, no subject can be regarded as finished, as in the block system.

FALLACY OF THE MARKING SYSTEM

Is not our real aim for the student to have him continue as a student during his lifetime? Circumstances which militate against this development are therefore objectionable because students are led to feel that in acquiring an A or B, day by day, their paper record as it grows in the hands of the quiz master is tantamount to a personal acquisition of knowledge. Hence the development of memory rather than of thought gains for a man the reputation of a real student. Further, the marking system forces students, too intelligent not to see the fallacy of the procedure, into at least a pragmatic acceptance of it. Again and again the most serious and well meaning will cut the classes and clinics in which they might be gaining valuable interests in order to cram a superficial, temporary memorization of facts necessary to attain "a good mark" in an announced test. Nor are they to be blamed; if the others set a standard for memorization, they feel they must follow, to get the "good mark"

which in so many cases is used as the basis for the judgment of a man's worth—as though it were anything but the poorest reflection of his true capabilities.

The passing mark of 75 per cent.—C, used in many colleges—is another vicious influence, especially when there are many marked tests throughout the year. It tends to make the student feel he need make but three quarters of effort, only clean three quarters of a table, or at amputation cut through but three quarters of the tissues, especially since such marks are obviously inadequate, representing in no way the instructor's thoughtful estimate of the student's work or ability. Similarly, the mark tends to stimulate some students to obtain surreptitiously from notes or neighbors facts for the written test or recitation. Would it not be of greater aid both to student and to teacher to use a shifting scale? Work would then be either "satisfactory" or "unsatisfactory," according to the teacher's estimate of the student's ability.

Like the marking system, the formal examination which calls for an assembly of concrete facts is particularly to be deplored. The student who has the greatest amount of mental surface tension, and who can balance the largest number of facts on the end of his pencil, is the victor in such a contest, regardless of his ability or inability to understand or make use of these facts.

COMPETITION AS A STIMULUS FOR STUDY

Nearly all teaching methods employ a goad of some form; and the one which tends to maintain the student's self respect is the best. It is foolish to blind one's eyes to the fact that, since the world was young, man has striven and succeeded in competition, and he has become weak and vegetative without such a stimulus. Where the annual practical examination in anatomy is in vogue, all students aspire to enter the group of those who make no mistakes. Such a distinction comes only to those who make no mistake in competition with themselves and anatomy. This method serves as a healthy goad to the acquirement of a knowledge of the subject. The exercise of this stimulus can be produced in all subjects, not alone in anatomy.

PRACTICE OF MEDICINE

Having considered teachers, students, methods of teaching and of study, it is necessary to formulate what

medical education is expected to give. The epoch of a morphologic, ultramechanical aspect of the living animal as a conception and basis for study is apparently passing. The substratum may be regarded as structural, but the correlation of functional activities must be regarded as the essence of life in an individual. Further, the biologist is insistent that derangement of functions brings about related functional changes and, progressively, alteration of structure. The progressive summation of functions and equilibration of structure constitutes the living individual. Students, however, are still led to think in mechanical terms and fail to realize that individual patients are not at all "closed systems." They are aware of the patient's environment, but have not a full conception of the interrelatedness and intrarelatedness of all energy phases even to the n th dimension. To make plain this concept of dynoplasm, coordination must be sought; the interdependence of all "normal" and "pathologic" conditions must be stressed that no graduate of a medical school shall go out with his knowledge walled off by interdepartmental barriers.

In essence, all are seeking what M. Louis so forcefully expressed to his pupils nearly a hundred years ago:

Such and such have been my observations. You can observe as well as I. If you will study the art of observation, and if you will come to it with an honest mind and be faithful in noting all which you discover, and not merely the things which are interesting at the moment, or those which support a favorite dogma. I state to you the laws of nature as they appear to me; if true, your observations will confirm them; if not true they will refute them; I shall be content if only the truth be ascertained.

Think how far the capable student could travel on the road to a good medical education in the allotted four years, if all the teachers of "departments" should together frame a carefully thought out course, topic by topic. Up to the present, the various departments in many schools, without a due recognition of one another's responsibilities in the teaching of medicine as a whole, have devised a system which fills the student's time completely. Is there any valid reason why this should continue? And yet it has continued and does continue, and every year the ruts are worn

negot and the vision of the future is more and more obscured by the piled up walls of habit.

Many things that have been said in the preceding pages are but platitudes and repetitions to those who are interested in medical education; but until in some way these foundation stones of education cease to be used as roofing and are put where they can be of real value—not in books or even in the minds of educators, but in the practice and curriculum of schools—clinical lecturers will continue to think they are showing a skin mole to a whole class, when it is so small they can hardly see it themselves. Instructors will continue to lay down the law of dogma, and wonder what is the trouble when interns fail to cope with emergencies not laid down in the books. And we shall continue to write articles on medical education.

CONCLUSIONS

Only the best instructors should be chosen, because on them depends the selection of students and to a large degree their development and education. The surest way to have many good instructors available is continuously to develop them from those possessing the greatest apparent potentialities.

Teachers who do not continuously prove of value should not be allowed to remain in a school.

The method maintained should aim for the selection and maintenance of good teachers and laboratory workers, for under them any method of education is successful.

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A STUDY OF DIVERTICULUM FORMATION IN THE APPENDIX *

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The subject of diverticulum formation in the appendix has apparently aroused the interest of but few writers in Europe and America. It seems rather astonishing in these days of experimental investigation of almost every conceivable subject that this interesting, if relatively unimportant, process has never, so far as I can ascertain, been produced or studied experimentally. Hypotheses have been based on morphologic observations of the appendix itself, together with the application to the appendix of a few experiments made in the large and small intestine. The results are unsatisfactory because some of them, reported by earlier observers, either could not be reproduced, or produced entirely different and contradictory results, when repeated by others.

It seems, therefore, that this condition deserves further investigation, particularly so inasmuch as I have become convinced during the past year that the condition is not nearly so infrequent as the few reported cases would lead one to believe. When, coincidentally with the change in the method of examining the appendixes in the laboratory of surgical pathology at the Presbyterian Hospital, we found five examples of diverticulum formation in the appendix in one year, whereas in the ten preceding years there was a record of only one appendix with a diverticulum, the inference is justifiable that many cases must have been overlooked. It was formerly our custom to make two or more transverse sections of the appendixes sent for examination, until the discovery of a case of multiple diverticula aroused our interest in making a careful search for this condition, and we began to section all the appendixes longitudinally in a plane passing through the mesenteric and anti-mesenteric borders. Four more appendixes came to our attention in this way, none of which were suspected or observed by the surgeons who removed them.

The questions which naturally arise in connection with diverticula of the appendix are: (1) Have they any clinical significance? (2) What are their morphologic characteristics and what are the factors which lead to their formation? (3) Is there any way in which they may be diagnosed clinically? (4) Can their formation be prevented, or, if they

*From the Laboratories of Surgery at the College of Physicians and Surgeons, Columbia University, and the Laboratory of Surgical Pathology, Presbyterian Hospital, New York. Drawings by Alfred Feinberg.

have formed, is any treatment indicated? Most of those who have written about diverticula of the appendix have concerned themselves almost exclusively with the second of these questions, while a few have speculated about the first. This paper will deal very largely with the second question.

The discussion which follows is based on (*a*) the study of seven appendixes with diverticula, six of which were removed operatively at the Presbyterian Hospital, New York, and one at necropsy at the Bellevue Hospital by Dr. B. Morgan Vance and kindly given to me by him for study; (*b*) the reexamination of a large number of appendixes removed operatively at the Presbyterian Hospital during the last eleven years, for certain morphologic and pathologic characteristics which seemed to have some bearing on the formation of diverticula; (*c*) certain experiments on dogs, the results of which are suggestive in attempting to determine some of the etiologic factors; (*d*) a study of all the literature to which I could obtain access, with the desire both to learn what other investigators have observed and deduced and to ascertain from the photographs and drawings reproduced whether certain morphologic peculiarities which are apparent in the series reported in this paper were also present in other appendixes.

Before attempting to analyze the factors which seem to favor the formation of diverticula of the intestinal tract in general and of the appendix in particular, it will be pertinent to define what is understood by the term and to review briefly the hypotheses which have been advanced up to the present to explain them.

DESCRIPTIVE DEFINITION, STATISTICS AND HYPOTHESES OF DIVERTICULUM FORMATION

Most writers are agreed that diverticula in the appendix are "evaginations," "protrusions," "herniations," etc., of the mucosa, muscularis mucosae and submucosa through defects in the muscular coat. They are all said to be of the "acquired" variety, in contradistinction to the congenital diverticula which may be found in the intestinal tract, such as Meckel's diverticulum, in the walls of which are to be found all the coats which are present in the wall of the intestine. Such congenital diverticula have never been noted in the wall of the appendix.¹ They may be single or multiple. They are most commonly found along the mesenteric border, bulging out between the leaves of the mesenterium. Less commonly, they occur along the antimesenteric border and at the tip; very rarely elsewhere. In regard to frequency,

¹ Kradel: Divertikelbildung bei Appendicitis. Beitr. z. klin. Chir. **80**: 121, 1912.

MacCarty and McGrath² report seventeen in 5,000 appendixes (0.34 per cent.), Konjetzny³ found two in 1,000 cases (0.2 per cent.), Moschcowitz,⁴ four in 1,500 (0.26 per cent.) and Mertens⁵ in 106 necropsies found two appendixes with diverticula, and in twenty-eight appendixes removed at operation, one diverticulum (together, 2.23 per cent.). If we take the five cases (Cases 1 to 5, inclusive) found in the one year, from July 1, 1921, to June 30, 1922, during which time 264 appendixes were removed at the Presbyterian Hospital, the percentage is 1.89.

The diverticula usually range in diameter from 3 to 5 mm. Rarely, if ever, do true mucosal lined diverticula reach a larger diameter than 1 cm., although mucocèles may reach a much greater size. They are evenly divided between males and females. The youngest patient apparently was Wilkie's,⁶ a 15 year old girl; while MacCarty and McGrath² found one in a patient 64 years old. Usually, they have been found in appendixes acutely or chronically inflamed; occasionally, they have been found at necropsy or in patients operated on for some unrelated trouble. Reference to the accompanying statistical table will reveal that the cases reported here conform to these observations without any important variations, except a morphologic one which will be referred to later.

Of the acquired type, two groups are recognized: (1) those that are said to occur through the defects in the muscular coats which are found along the mesenteric and antimesenteric borders of the appendix, and through which pass the vessels which supply the submucosa and mucosa, and (2) those which occur through defects in the muscular coats which are results of acute inflammatory processes. Thus, there may be an intramural abscess which destroys the muscularis but which heals without perforation, leaving a scar in the muscularis through which the protrusion may subsequently occur; or there may be perforation with protrusion of the mucosa at the same time and, subsequently, subsidence of the acute inflammatory process without removal of the appendix. The last process may lead to the formation of an external mucocèle, i. e., a subserous or intramesenteric collection of mucus in a cavity lined

2. MacCarty, W. C., and McGrath, B. F.: Clinical and Pathologic Significance of Obliteration, Carcinoma and Diverticulum of the Appendix, *Surg. Gynec. & Obst.* **12**:211 (March) 1911.

3. Konjetzny: Zur Pathologie und Klinik der erworbenen Wurmfortsatzdivertikel, *München. med. Wchnschr.* **56**:2251, 1909.

4. Moschcowitz, E.: The Pathologic Diagnosis of Diseases of the Appendix, *Ann. Surg.* **63**:697 (June) 1919.

5. Mertens: Falsche Divertikel, etc., *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **9**:743, 1902.

6. Wilkie: Carcinoma of the Appendix Causing Diverticula of the Appendix and Acute Appendicular Obstruction, *Brit. J. Surg.* **8**:392 (April) 1921.

with connective tissue which communicates with the lumen of the appendix by a tract lined with mucous membrane extending through the muscularis.⁷

All of the foregoing statements are based on morphologic observations. The diverticula have been seen, and, as they were all accompanied by defects in the muscularis, it was assumed that muscular defects must precede their formation. The only muscular defects which could be found were those through which the vessels passed and those which were the result of damage following infection; ergo, the diverticulum must take place through these defects.

In order to explain why protrusions of mucous membrane occur through these defects in some appendixes and not in others, various hypotheses have been advanced. Most of them were used in an attempt to explain the occurrence of diverticula in the intestine, but they have been applied to those occurring in the appendix as well.

Klebs⁸ states that, in obese people, collections of fat about the vessels as they pass through the wall tend to shove the muscle bundles apart, thus increasing the diameter of the defect and increasing its potential weakness. Graser⁹ suggests that the chronic distention of the blood vessels as they pass through the muscular coats tends to push aside the muscle bundles, in this way increasing the diameter of the defect.

Practically all of the authors who attempt to account for the force which tends to drive the mucosa and submucosa through the muscularis speak of increased intraluminal tension. Edel¹⁰ suggests chronic constipation with fecal distention of the large bowel as a source of this increased tension. Beer¹¹ believes that, in addition to constipation and chronic distention of the large bowel, it is necessary to have the muscular degeneration and weakness which are coincident with old age. Wilkie⁶ states that the obstruction of the lumen of one of his appendixes by a carcinoma was sufficient to explain the occurrence of a diverticulum distal to it.

When one attempts to analyze these hypotheses and apply them to appendix diverticula, it is found that, while each one of them may be applicable to a few cases, none of them has a universal application. Klebs⁸ suggests that the vascular defects in the muscularis are

7. Kujala: Sur un cas d'appendicite chronique avec pseudo-myxoma diverticulaire. Bull. de l'Acad. de méd. **79**:175, 1819.

8. Klebs: Path. Anat., 1869, p. 271.

9. Graser: Ueber multiple falsche Darmdivertikel in der Flexura sigmoidea. Monathshefte f. Weibchenheilk. **46**:721, 1899.

10. Edel: Ueber erworbenne Darmdivertikel. Virchows Arch. f. path. Anat. **138**:347, 1894.

11. Beer, E.: Am. J. M. Sc. **128**:135 (July) 1904.

increased in diameter by accumulations of fat about the vessels obviously loses its force when the diverticula occur, as they usually do, in people who are not obese. Graser's hypothesis that chronic distention of the blood vessels in the vascular defects tends to shove aside the muscle bundles, thus increasing the diameter of the defects, does not apply to any of the appendixes with diverticula that I have seen or read about. In these, where there have been broad defects, they have been filled with dense connective tissue, surrounding several rather small and thick walled vessels, which were not distended. It might be argued that these had collapsed after removal, but a majority of the appendixes which we receive for examination in the laboratory reach it with their vessels distended; so this is probably not a valid objection. In any event, this hypothesis has no bearing on the inflammatory defects. There is no proof that chronic constipation and fecal distention per se cause increased intraluminal tension, and it can be definitely stated that diverticula of the appendix at least may occur in people in whom there is no clinical evidence of chronic constipation or fecal accumulation in the large bowel. Beer's suggestion that weakening of the muscle, due to old age, is an etiologic factor is rarely applicable to the appendix diverticula, most of which occur in vigorous adults, and examination will show that the muscular coats are, in almost every case, above the average in thickness. It is probably true that there is some obstruction to the lumen proximally in a majority of appendixes with diverticula; but there are just as certainly others in which there is no demonstrable obstruction, and, therefore, this cannot be regarded as an etiologic factor of universal application.

The importance of increased hydrostatic tension within the lumen of the intestine as a factor in the etiology of diverticula of the intestine (and, by inference, of the appendix) received strong support through the publication, in the latter part of the nineteenth century, of some experimental work that has since been completely discredited, but the influence of which can still be traced in recent articles on the subject. Heschl,¹² Hansemann¹³ and Grassberger¹⁴ distended segments of the large intestine with water, and asserted that they saw bulgings along the mesenteric border, which disappeared when the tension was released. They asserted that these occurred at the defects in the mesenteric border through which the vessels pass, and they argued from this that these were weak points through which diverticula might occur in the living intestine, if the increased intraluminal tension were chronic. Beer¹¹ was

12. Heschl: Wien. med. Wchnschr. **30**:1, 1880.

13. Hansemann: Ueber die Entstehung falscher Darmdivertikel, Virchows Arch. f. path. Anat. **144**, 1896.

14. Grassberger: Ein Fall von multiplex Divertikelbildung, Wien. med. Wchnschr. **10**:149, 1897.

unable to reproduce these bulgings experimentally, and it is probable from Chlumsky's observations that they are at best a phenomenon of dead intestine only. Heschl,¹² Hanau¹⁵ and Good,¹⁶ using human necropsy material, several hours after death, found that, after extreme distention, the intestine burst regularly between the leaves of the mesentery. This observation has been used as an argument to support the hypothesis that the mesenteric border is the weakest portion of the intestine wall, and that perforations and diverticula are therefore more liable to occur in this region than in any other. Chlumsky,¹⁷ however, showed the fallacy of using dead material for investigation by repeating this experiment, using the living dog's intestine within the body. He found that it burst regularly along the antimesenteric border. When he used dead intestine, removed from the body, he found that it burst between the leaves of the mesentery. We are thus left with inconclusive evidence, so far as these experiments are concerned, when we attempt to apply them to determine the forces which tend to produce diverticula in the appendix and the intestine.

The only observations which, it seems to me, can altogether survive critical analysis are the morphologic ones that diverticula are always associated with defects in the muscularis and that the only defects which have been observed are those due to perforation, to scarring following suppurative inflammation and the normal ones in the mesenteric and antimesenteric borders through which vessels pass. There is no proof that diverticula occur through these defects; but all the evidence that we have favors the assumption that they do, and, therefore, it seems fair to accept it as a working hypothesis.

If we turn now to the seven appendixes described in this paper, a reference to Figures 1, 2, 3, 5 and 6 demonstrates very clearly a condition which has not been described before in the literature, possibly because in most of the cases reported the specimens were sectioned transversely instead of longitudinally. In these diverticula, it will be seen that, not only the mucosa and submucosa nearest the muscular defect have passed through it to form an extra muscular sac but also the mucosa and submucosa from the side opposite the muscular defect have passed through it, thus, in effect, diverting the entire lumen outside the appendix into the diverticulum sac.¹⁸ This condition was noted in four diverticula in four different appendixes out of a total of eighteen

12. Heschl: *Fallende Darmdivertikel*. Virchows Arch. f. path. Anat. **138**, 1894; *ibid.* **145**:172, 1896.

15. Good: *An den Leichenhaus des Cantonspitals zu Gallen* (Dr. Hanau). Inaug. Diss., Zurich, 1894.

17. Chlumsky: *Ueber verschiedene Methoden der Darmvereinigung*, Beitr. z. klin. Chir. **25**:539, 1899.

18. Several of the diverticula illustrated by MacCarty and McGrath (Footnote 2) seem to show this condition, but no reference is made to the phenomenon in the text.

diverticula in seven appendixes. The same diversion of the lumen outside the muscularis can be seen in the appendix which had ruptured two years before it was removed, eversion of the mucosa into an abscess cavity resulting, with the proximal and distal portions of the appendix opening into it separately through the muscular defect (Fig. 13).

All of the hypotheses which have been advanced to account for the motive force which pushes the mucosa through the muscular defects depend on a distention of the lumen. The existence of these four diverticula, however, forces us to seek some additional explanation to account for them. It is inconceivable, for me at least, to imagine that the force exerted by the expansion of a fluid or a gas within the lumen of an appendix could *alone* be sufficient to force the entire circumference of the mucosa and the submucosa through a defect in the muscularis. Some other force must be operative in these cases and probably in all the rest of the cases of diverticulum formation as well.

A little reflection will make it apparent that most of the comments and reasoning up to this point have been based on morphologic and mechanical considerations almost exclusively. We have talked of diverticulum formation as if it took place by the action of a force in an inert, lifeless tube made up of tissues of different tensile strength but without any other characteristics. This neglect of the biologic factor has resulted in the neglect of the tremendous energy transformations which are occurring constantly in the appendix and intestine throughout life; it has allowed constant morphologic references to the smooth muscle tissue of the appendix but scarcely any physiologic ones.¹⁹ In other words, the force exerted by the contraction of the smooth muscle tissue in the appendix during life has not yet been considered as an important factor in the etiology of diverticulum formation.²⁰

MORPHOLOGIC AND EXPERIMENTAL EVIDENCE IN FAVOR OF THE MUSCULAR CONTRACTION HYPOTHESIS OF DIVERTICULUM FORMATION

Inasmuch as no one, as far as I can find out, has investigated the possibilities of this force in connection with appendiceal diverticula, it

19. Seelig (Footnote 26) in a single phrase suggests that the contraction of the smooth muscle plays some part in diverticulum formation in the appendix, but does not develop the theme.

20. It is all the more astonishing that this should be so when one finds that it has been considered in reference to diverticula elsewhere in the body. Forty-five years ago, Zenker (quoted by Judd: Esophageal Diverticula, Arch. Surg. 1:38 [July] 1920) described the pharyngo-esophageal dimple just behind the cricoid cartilage on the posterior wall, where there is a weakened point due to the arrangement of the musculature at the junction of the upper esophagus and the lower end of the pharynx. He noted that diverticula occur through this, and believed that the increased pressure exerted on the weak point during the act of swallowing was the chief etiologic factor.

seemed as if it were worth attempting. With this purpose it was determined to state a theorem in regard to diverticulum formation and then to see whether it would serve to explain all the known phenomena. If it did so this would not prove it true, because we know by observation only a few of the phases of the process. If supported by the facts, however, it would make it at least a more satisfactory hypothesis than any which has been advanced before, because, as has been indicated, none of them serve to explain all of the known phenomena.

It has been assumed, therefore, that diverticula take place through defects in the muscular coats, and that the chief motive force that drives the submucosa and mucosa through these defects is that exerted by active contraction of the longitudinal and circular muscles on the submucosa, mucosa and contents of the lumen. With this in mind, a morphologic examination of a number of appendixes has been made and certain experiments have been performed, with the hope that the results would suggest whether the hypothesis was credible or not.

In order to understand the process of diverticulum formation, it is necessary to emphasize certain well known mechanical and physiologic facts. One must first recall the physical relationship which the coats of the appendix bear to one another. The mucosa and the submucosa, with the muscularis mucosae running between, form a single coat, the three parts of which are intimately bound together. The muscularis, subserosa and serosa likewise form a more or less homogeneous whole. But, in many appendixes, especially those which have not been previously badly damaged by inflammation, the attachment between the submucosa and muscularis is by loose bonds of areolar and elastic tissue, so that the two coats are capable of a certain amount of excursion, one upon the other.

The muscular coats of the appendix are divided into an outer longitudinal coat and an inner circular coat, the latter usually much thicker than the former. Under normal conditions of tonus, unless widely distended by inspissated feces, fluid or a fecolith, the mucosa and submucosa in many appendixes are maintained within the circular muscle in a plicated state, both transversely and, to a less extent, longitudinally. When there is a loose attachment of the submucosa to the muscularis, it allows free play between these two coats. With strong muscular contractions, the tendency is to exaggerate these folds by reducing both the diameter and the length of the appendix. If an appendix or intestine is fixed in a state of strong muscular contraction and then sectioned longitudinally, these exaggerated folds can easily be seen.

With these observations in mind, let us suppose that there is a weak point in the muscular wall of the appendix and the muscle contracts: what may happen? In order to answer this question, we are forced to use animals, because it is improper to use the living human appendix in

situ for experimental purposes. While dogs' appendixes are too much like exaggerated cecal pouches to be altogether satisfactory for experimental purposes, I was forced to use them because I was unable to procure organs more nearly resembling the human. Reference to Experiments 1 to 5 will show that, if a muscular defect is made in the wall of a dog's appendix by incising down to the submucosa or by excising a piece of subserosa and muscularis, there is, following the injury, a strong contraction of both circular and longitudinal muscles, and, at the same time, the mucosa and submucosa protrude through the muscular defect, forming a diverticulum.²¹ This can persist for some days. If the same thing is done to an appendix sufficiently long after death for the muscular tissue to lose its contractility, no such protrusion will occur, *provided the appendix or intestine is not distended*. If it is distended, the protrusion may occur (Experiment 5).

From these experiments, we see that, with a suddenly produced unfilled gap in the muscularis of a dog's appendix or intestine, because of the free play between the submucosa and the muscularis, the mucosa and submucosa may be protruded by muscular action and may also be protruded by the force of fluid tension acting from within the lumen. We can go a step farther in studying the effects of muscular contraction and distention. If an appendix with a protrusion of mucosa and submucosa through an experimentally produced gap in the muscularis due to muscular contraction is distended moderately, the diverticulum fills with fluid and stands out more clearly as a smooth rounded hemisphere. If the internal hydrostatic tension is considerably increased, the diameter of the appendix gradually increases, the coats of the appendix become thinner as they are stretched, the gap in the muscularis increases in width and the *diverticulum grows steadily less until it disappears entirely* (Experiment 4). This effect is produced apparently because the increased internal hydrostatic tension overcomes the force of muscular contraction and stretches and thins the muscular coats until they are forced outward to as great a distance as the original diverticulum. In a dog's dead intestine, in the body, increased intraluminal

21. When this procedure was repeated, using a human appendix which had just been removed from the body and which showed very moderate chronic inflammatory changes, the same bulging of the mucosa and submucosa through the muscular defect occurred. In this case, the bulging was only 1 mm. beyond the serosal level (Experiment 6). Some years ago, when Dr. Lewisohn (Clinical and Experimental Studies on Congenital Pyloric Stenosis, Surg., Gynec. & Obst. 26:320 [March] 1918) was doing some experimental Rammstedt operations on the dog's pylorus, in one case, the operation was followed by diverticulum formation. It seems probable that, in this situation, it was due more to muscular contraction than to distention, as the pylorus is probably very rarely distended (compare illustration in his article).

tension at first forces the mucosa and submucosa out through the gap in the muscularis, making a diverticulum; with marked increase in the tension, the appendix dilates enormously, and the diverticulum disappears as described above (Experiment 5).

We are now in a position to state that a diverticulum may occur through an experimental defect in the muscularis of a dog's appendix, both as the result of intraluminal distention and as a result of muscular contraction. Increased muscular contraction increases the tendency for the mucosa to be protruded, while greatly increased intraluminal tension tends to diminish and, eventually, to cause the disappearance of the diverticulum.

With these suggestive animal experiments in mind, let us turn back to the human appendix to see whether a morphologic consideration of a number of appendixes will support the hypothesis that muscular contraction is the chief factor in the causation of diverticula of the appendix and, at the same time, strengthen the view that in many cases the vascular defects are the weak points in the muscularis through which the protrusions occur.

The arteries and veins which supply the appendix reach that organ at from six to eleven different points along the mesenteric border. They send branches that pass through the muscular coats and form a rich anastomotic network in the submucosa. Other branches pass circumferentially in the subserosa, and, at the antimesenteric border, these also pierce the muscular coats and join the submucosal anastomosis. A few small twigs pass into the muscularis between the mesenteric and antimesenteric borders; but they are apparently for the supply of the muscularis itself and do not pierce it. The vessels as they pass through the muscular coats are surrounded by a greater or less amount of connective tissue and sometimes by a few fat cells. When seen, these vascular defects are always larger and much more prominent on the mesenteric than on the antimesenteric border. Usually, the vessels pass through at right angles to the long axis of the appendix; less often, they pass through tangentially. When found in the appendixes examined, they varied between 0.5 and 1 mm. in thickness on the mesenteric border, and were always less than 0.5 mm. on the antimesenteric border.

In examining the appendixes with diverticula in the series reported in this paper, it was noted in all of the cases that the muscular coats appeared above the average in thickness, while in all but one the vascular defects were very prominent and easily visible.²² An attempt was made to determine the relationship between the width of the vascular defect

22. In the one exception, the diverticulum was believed to have followed an inflammatory weakening of the wall rather than to have occurred through a vascular defect (Case 7).

and the thickness of the musculature in the appendix. Ninety-six appendixes were chosen at random as they were received in the laboratory of surgical pathology, and the thickness of the muscular coat was measured by a millimeter scale. The average thickness was 0.86 mm., a figure slightly above the 0.5 to 0.75 mm. which Aschoff²³ says is the variation in normal adult appendixes. During the routine gross examination of these appendixes, it has been a laboratory rule that the appendix shall be bisected longitudinally in a plane passing through the mesenteric and antimesenteric borders, and the presence or absence of the vascular defects noted in the report. When the defects are of any size, the vessels are surrounded by dense connective tissue, which shows up as a dull white band, in sharp contrast to the much darker semi-translucent muscularis. It is not unreasonable to assume, therefore, that, in those cases in which the defects were seen, they were probably broader and contained more connective tissue than in those in which they were not seen. In the forty-two cases in which they were seen, the average thickness of the muscularis was 1.06 mm. (the thinnest, 0.5, and the thickest, 3.0 mm.); while in the fifty-four cases in which the vascular defects were not seen, the average thickness of the muscularis was 0.71 mm. (the thinnest, 0.3, and the thickest, 1.5 mm.).²⁴ The average diameter of the vascular defects in the mesenteric border in the forty-two cases in which they were seen was 0.5 mm.

Turning to the series of seven appendixes with diverticula, we find the average width of the muscularis 1.91 mm. (the thinnest, 1, and the thickest, 2.7 mm.). In Cases 1 to 6, inclusive, in which the mesenteric vascular defects were noted passing through the muscularis, the average diameter of the largest defects noted in each case was 1 mm. (the largest, 1.5, and the smallest, 0.5 mm.).

These figures suggest that appendixes vary considerably in the thickness of their muscular coats and that the broader vascular defects which are more easily visible with the naked eye are found in the more thickly muscled appendixes. They also indicate that the muscularis of those appendixes in which diverticula are formed averages a whole millimeter thicker than in the average appendix removed at operation, and that the mesenteric vascular defects in the appendixes with diverticula tend to be broader than the average.

We cannot satisfactorily account for this muscular thickening in every case by the hypothesis that it is hypertrophy resulting secondarily

23. Aschoff, L.: *Die Wurmfortsatzentzündung*, Jena, 1908, pp. 10 and 72.

24. Of course, these figures have only comparative value because of the many variables and sources of error, the greatest being the edema of the muscularis in acute cases. But, as the same factors of error are operative in both series, it is felt that the value of the results for comparison is not vitiated.

from obstruction of the lumen and increased function of the muscular tissue, this increased function being stimulated by accumulation of contents within the lumen, because, while in five of the seven cases there was either actual or potential obstruction of the lumen proximal to the diverticula, in two (Cases 4 and 6), there was neither, and both of these had thick muscular coats. So, while admitting the attractions of this hypothesis and suggesting with Wilkie⁶ that it plays some part, it must be admitted that some other factor or factors are involved. In any event, one cannot escape from the suggestion that these thick muscles indicate increased function and that they are capable of more powerful contraction, and hence of exerting a more powerful force, than the thinner ones.

It will not be unprofitable, at this point, to reconsider the question of diverticulum formation as a result of damage to the wall of the appendix from suppurative inflammation. As we have seen, it has been stated, first, that an intramural abscess may form, destroy the muscularis, drain into the lumen of the appendix, and subsequently be replaced by scar tissue, thus leaving a defect through which it is conceivable that a diverticulum may pass; second, that, during an acute inflammatory attack, the appendix may perforate, and, as a result of the perforation, a diverticulum or mucocoele may develop. All that can be adduced to support the first statement are the observations that intramural abscesses occur; that scars occur in the muscularis, and that diverticula occur. All of the intervening steps are suppositious. In regard to the second, however, we are able to demonstrate more of the intervening steps, and it will be worth while to do this because of the light which it seems to throw on the dynamics of the process.

It must be recalled that the vast majority of perforations of the appendix are associated with extensive necrosis of the mucous membrane. Most perforations appear as holes lined with necrotic tissue, leading through the wall from a lumen also largely lined with necrotic tissue. Occasionally, however, we find the condition of affairs illustrated in Figure 12, in which there is a wide perforation without extensive necrosis, which has resulted in the protrusion and eversion of the mucosa and submucosa (Case 8). A condition analogous to this, but of two years' standing, can be seen in Figure 13, which has been referred to before. There we find perforation, with protrusion through the perforation not only of the adjacent mucosa but also of the entire lumen, so that the proximal and distal portions of the lumen open separately into the extra-appendiceal abscess (Case 9).

Figure 4 presents a tract lined with mucous membrane leading to a cavity in the mesenterium near the tip, filled with mucus and pus and lined with granulation tissue. As there is a diverticulum in another part of this appendix, this may be thought of either as a diverticulum in

which the acute inflammatory process has destroyed its lining mucosa or (and this appeals to me as more probable) it may be considered that, as the result of an acute inflammatory process in the appendix wall, possibly during a previous attack, a perforation and partial protrusion of the mucosa occurred with the formation of a mucocele, and that the inflammation present when the appendix was removed involved a previously formed sac.

The speed and ease with which mucosal defects in the intestine can regenerate is well known, so that it requires no great stretch of the imagination to surmise that, in Cases 8 and 9, had there been a subsidence of the infection, perhaps by free and adequate drainage of the abscess through the fistulous tract leading back through the wall of the appendix into the lumen and so on into the cecum, a regeneration of mucosa might have lined the extramucosal sacs, giving the picture seen in other diverticula in this paper; in the latter case with a single opening into the lumen, in the former with a double opening. Figure 11 illustrates a diverticulum near the tip of an appendix that may very well have occurred in this way.

Figure 12 illustrating a fresh perforation, with protrusion of the mucosa and eversion, cannot fail to recall, to all who have seen it, the behavior of the mucosa of any part of the living gastro-intestinal tract when the entire thickness of the wall is cut through and the lumen entered. It will be remembered that, coincidentally with the wide gaping of the wound, the mucosa protrudes and, as it comes out, turns back on itself so that it both projects beyond the surface of the serosa and still allows the cut edge of the mucosa to lie in contact with the cut edge of the serosa. If the same cut is made in a dead intestine, none of these phenomena occurs. In this case, we cannot blame the intraluminal tension; for, as soon as the lumen is entered, the intraluminal and extraluminal tensions are equalized. We are therefore compelled to fall back on the force of muscular contraction which responds to the irritation incident to the trauma of the incision. The segment cut into is narrowed and shortened by the contraction of the circular and longitudinal fibers, which, in turn, forces the redundant mucosa and submucosa through the opening; and, because the submucosa is attached to the muscularis while the mucosa is a free, unrestrained surface, eversion occurs. The similarity between this experimental end-result and the perforations illustrated in Figures 12 and 13 is so striking that I believe we are justified in adopting the hypothesis that the force resulting from muscular contraction is the chief factor in producing the eversion of the mucosa and submucosa.

SUMMARY

The foregoing reexamination of the process of diverticulum formation in the appendix has set forth some experimental evidence and

some morphologic facts, all of which have tended to support the muscular contraction hypothesis with which we started, and none of which have contradicted it. To recapitulate, it has been shown that there must be a weak point in the wall of the appendix which is probably due either to an especially broad vascular defect in the mesenteric or antimesenteric border filled with connective tissue, a condition found in most appendixes with diverticula; or to a scar in the muscularis, the result of a suppurative process; or to perforation during an acute attack, with protrusion of the mucosa and subsequent subsidence of the infection followed by regeneration of the mucosa within the former extramucosal abscess cavity.

It has been suggested that, in all forms of diverticula without exception, contraction of the circular and longitudinal smooth muscle coats is probably the chief active factor in driving the mucosa and submucosa through the weak point in the muscularis. In support of this, there is the morphologic evidence that, in all seven of the cases reported, the muscularis is above the average in thickness. In five of these, this is associated with more or less obstruction of the lumen proximally either by intraluminal mechanical means, complete obliteration, twists or angulations. In the other two, no obstruction could be demonstrated, but it was possibly present during life. Usually, this obstruction is accompanied by dilatation of the lumen, distal to it. There is also the condition of complete diversion of the lumen outside the muscularis into the diverticulum sac, which can be explained best by the muscular contraction hypothesis.

By experiment on dogs' appendixes, it has been demonstrated that operative muscular defects result immediately in protrusions of mucosa and submucosa accompanied by active contractions of the circular and longitudinal muscles, and that, when the muscles have lost their contractility, no protrusion will occur, if the lumen is empty. It has also been shown that moderate distention of the lumen will result in a similar protrusion, while extreme distention results in obliteration of the diverticulum.

From the foregoing data, the following attempt has been made to reconstruct the process of diverticulum formation. An appendix in which a diverticulum occurs must be thought of as a muscular tube above the average in thickness, and, because increase in structure connotes increase in function, capable of unusually powerful contraction, both longitudinally and transversely. It always contains submucosa, muscularis mucosae, mucosa and more or less material within the lumen. These different elements are relatively inert and should be thought of as the contents of the muscular tube, even though some of them are loosely attached to its inner surface. If such a muscular tube contracts, it becomes a potentially closed cavity, and there is exerted a

strong pressure on the contents, which may be considered as fluid, and so governed by the laws of hydrostatics. If there is a weak point in the muscular tube incapable of withstanding this transmitted force, it must yield, and the contents will protrude through the gap to a point where the driving and resisting forces become equalized. Depending on the balance between these two forces, the protruded elements may consist only of mucosa and submucosa immediately adjacent to the defect, or they may consist of the entire contents of the muscular tube in the segment containing the defect. In the former case, there will be a diverticulum consisting of a simple pouch lined with mucous membrane; in the latter, complete diversion of the lumen into the diverticulum sac.

REPORT OF CASES

APPENDIXES WITH DIVERTICULA

CASE 1.—July 3, 1922, a specimen was removed at necropsy by Dr. B. M. Vance from a woman, aged 46, whose history was unknown (medical examiner's case).

Gross Examination.—The specimens were the cecum, ascending colon, terminal ileum and appendix. The appendix was about 6 cm. long and sinuously curved. Near its base a band extended from the parietal peritoneum to the mesentery of the appendix. Almost opposite this, another broad band extended from the terminal ileum and its mesentery to the appendix and its mesentery. These were probably congenital. The appendix varied in diameter from 5 mm., near the base, to 10 mm., just beyond the middle. When the cecum was distended, apparently no fluid passed into the appendix. The distal half of the appendix had a free mesentery, containing a considerable amount of fat. In this could be seen, buried in fat, two hemispheric bulgings, which were apparently continuous with the mesenteric border of the appendix.

A longitudinal section revealed that the lumen in the proximal part was patent, but measured only about 1 mm. in diameter and contained a small amount of thick, slimy greenish material. At a distance of 3.7 cm. from the cecal-appendiceal junction, the lumen came to an abrupt termination after being diverted to one side. A thin septum separated it from the terminal portion of the appendix, where the lumen was widely dilated up to 5 mm. and filled with thick, white flocculent material. In this portion of the appendix, there were two defects in the muscularis of the mesenteric border, through the more proximal of which a protrusion of mucosa and submucosa had occurred for a distance of 4 mm. Through the more distal gap, not only had the mucosa and submucosa of the same side protruded, but also all the rest of the mucosa and submucosa of that region, so that the entire lumen had come to lie outside the appendix, within the sac of the diverticulum. From the diverticulum, the lumen passed back within the surrounding muscular coats once more in its course toward the tip, becoming markedly constricted as it did so. At the tip itself, there was a third defect in the muscularis through which the mucosa and submucosa passed, dilating up to 3 mm. to form a terminal diverticulum, which was surrounded by the mesenteric fat at the tip. The muscular coat of the appendix throughout was thick, averaging from 1.5 to 2 mm. The vascular defects in the mesenteric border were for the most part slender white lines about 0.3 mm. thick; one, however, measured 1 mm. (Fig. 1).

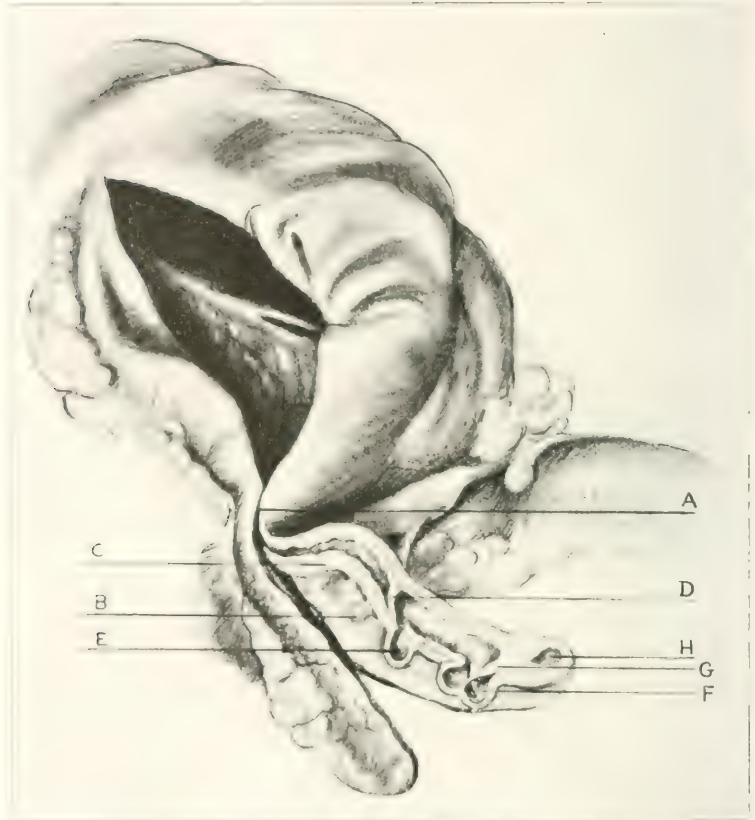


Fig. 1 (Case 1). Appearance of necropsy specimen from a woman, aged 46, with unknown history. The appendix has been bisected longitudinally. *A* is the junction of the appendix with the cecum; *B* the mesenteriolum. The muscular coat *C* is easily distinguished, by its darker appearance, from the whole appearing mucosa and submucosa. At *D*, a septum of mucosa and submucosa narrows the lumen and diverts it toward the mesenteric border, so that the proximal portion of the lumen is completely separated from the distal. Beyond this, the lumen is widely dilated, and the mucosa and submucosa pass through a defect in the mesenteric border forming the simple pouchlike diverticulum *E*. At *F* is another diverticulum with complete diversion of the lumen outside the muscular coats. The septum of submucosa and mucosa *G* appears complete in the plane of the section, but there was a small hole in it through which the continuity was maintained, indicated by the black marker in the diverticulum. *H* is a diverticulum at the tip.

Microscopic Examination.—Sections from the terminal diverticulum revealed that the sac of submucosa and mucosa projected for only a short distance through the muscular defect. It was intimately adherent to the surrounding fat, and there were many dilated veins immediately about it. The mucous membrane lining the sac was thin and poorly supplied with glands, and the submucosa showed only an occasional small lymph follicle. Sections of the large diverticulum into which the lumen was diverted confirmed the gross findings in every way. The thin septum which passed from the wall of the appendix opposite the muscular defect, through and completely across the diverticulum to its apex, was composed of a central core of submucosa lined on both sides by mucosa. As in the diverticulum, at the tip the mucosa was thin and poorly supplied with glands, and the submucosa contained only an occasional lymph follicle. The subserosa was everywhere thick and well supplied with dilated blood vessels. The muscular coats appeared thick and intact, and were without evidence of previous inflammation.

CASE 2.—History.—F. K., man, aged 30, married, a German fireman, suffered from cramps and vomiting for three days. He had had no previous similar attacks, and was never constipated. There was tenderness, and a mass was palpable in the cecal region. The temperature was 99.4 F. The white blood cells numbered 15,400; polymorphonuclears, 83 per cent.

Operation (Dr. Joelson, supervised by Dr. W. B. Parsons).—May 27, 1922: The appendix was acutely inflamed, laterad to the colon, extended up along the right side of the cecum, and was bound down by recent fibrinous adhesions. It was excised from the tip back, and the wound was drained. Recovery followed. June 12, 1922, there was a small granulating area still unhealed in the abdominal wound. Otherwise the patient was well.

Gross Examination.—The specimen was about 12 cm. long. It was slightly angulated at the junction of the proximal and middle thirds. The proximal third was about 9 mm. in diameter. Beyond this, it plunged into an adherent swollen mass of fatty tissue, which was dusky red and covered with a flaky, fibrinous exudate. The diameter of this mass was 2.6 cm. on the average (the appendix itself in this portion measured 1.7 cm. in diameter); 1.2 cm. from the base, there was a rounded, bulbous excrescence, slightly pedunculated and averaging 1 cm. in all diameters, projecting from the mesenteric border. It was soft and reddened and had infiltrated fibrous tissue and fibrin adherent to its dome.

On longitudinal section, the appendix was found to be divided into three sharply defined zones. In the *proximal portion*, the lumen was a narrow slit less than 1 mm. in diameter and apparently empty. It extended in a straight line for a distance of 1.5 cm., until it reached a point opposite the middle of the diverticulum, where it bent sharply at a right angle toward the mesenteric border and, accompanied by the mucosa and submucosa of both the mesenteric and antimesenteric borders, passed through a broad defect in the thick muscularis. Here, it joined, by a mere potential slit, the *second portion* of the appendix. Beyond this slit, the lumen was abruptly dilated, forming the main cavity of the diverticulum. The lumen then passed back through the same defect in the muscularis, where it was somewhat narrowed and, turning again at a right angle, resumed its course along the center of the long axis of the appendix. This portion was 1 cm. from the apex of the diverticulum to the center of the appendix and 2.5 cm. along its long axis. It was filled in this portion with thick pale creamy material under slight tension. The muscularis in this portion had been torn away along the mesenteric border for a short distance, probably by operative trauma. The second portion ended abruptly as

a blind pouch, the lumen at this point being completely separated from the distal portion. The *third portion* comprised a dilated lumen filled with bloody pus and lined with necrotic, hemorrhagic granulation tissue. There were two broad defects passing through the muscularis at the mesenteric border which seemed to be composed of reddened, congested fibrous tissue. The broadest was 1.2 mm. One similar, but much more slender, fibrous thread passed through the muscularis of the antimesenteric border. Surrounding the distal half was the tremendously thickened edematous fat of the adherent mesentery. On making further sections through the tip longitudinally, another diverticulum was revealed, with a neck passing through the muscularis about 1 mm. broad, beyond which was a cavity 3 mm. in diameter in the surrounding mesenteric fat. At its thickest part, the muscularis measured 1.5 mm. in width. The width of the broadest vascular defect was 1.2 mm. (Fig. 2).

Microscopic Examination.—The section through the large diverticulum, near the base, revealed that it was lined with flattened mucous membrane and that the thick, creamy material filling it was made up almost exclusively of

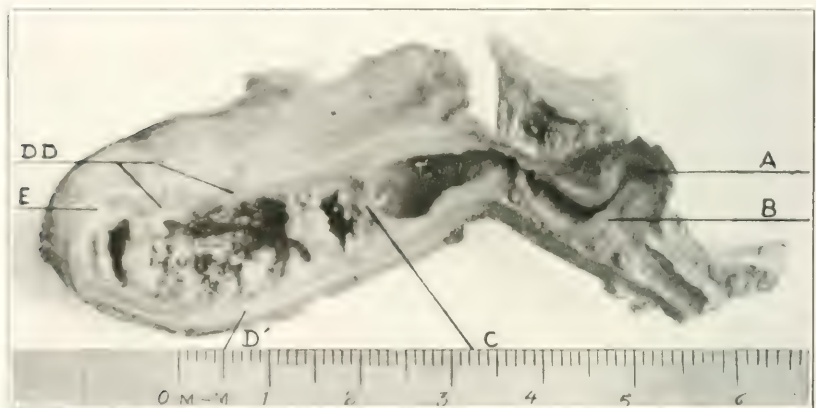


Fig. 2 (Case 2).—Appearance of an acutely inflamed appendix from a man, 30 years old. There were no previous attacks. At *A* is shown a diverticulum in the mesenteric border near the base, with complete diversion of the lumen of the appendix into the diverticulum, because of the projection of the tongue of mucosa and submucosa *B* through the muscular defect (compare Fig. 3). At *C*, the lumen is completely interrupted by a septum of connective tissue, beyond which there is partial necrosis of the mucosa coincident with the acute inflammation. *D* and *D'* are two vascular defects filled with connective tissue in the muscularis of the mesenteric border; *D'* is a similar defect in the muscularis of the antimesenteric border; *E*, region from which Figure 4 has been made.

leukocytes. The dilated central portion of the appendix which was continuous with this diverticulum was lined with a mucosa of similar type. The mucosa of the proximal portion was more normal in appearance. The neck of submucosa which extended from the antimesenteric side of the appendix through into the diverticulum was composed only of fibrous and fatty tissue, which was covered by the muscularis mucosae and mucous membrane. The diverticulum was covered exclusively by submucosa and muscularis mucosae, outside of which was adherent fatty tissue. A vessel of considerable size passed down

alongside the neck; which suggested that the diverticulum occurred in one of the normal vascular defects in the muscularis of the mesenteric border (Fig. 3).

Sections from the tip of the appendix revealed that the mucosa was extensively destroyed by a suppurative process. Where it was preserved, it was represented by a single layer of columnar cells, with only a few short mucous glands scattered at intervals between them. At a point opposite the abscess,

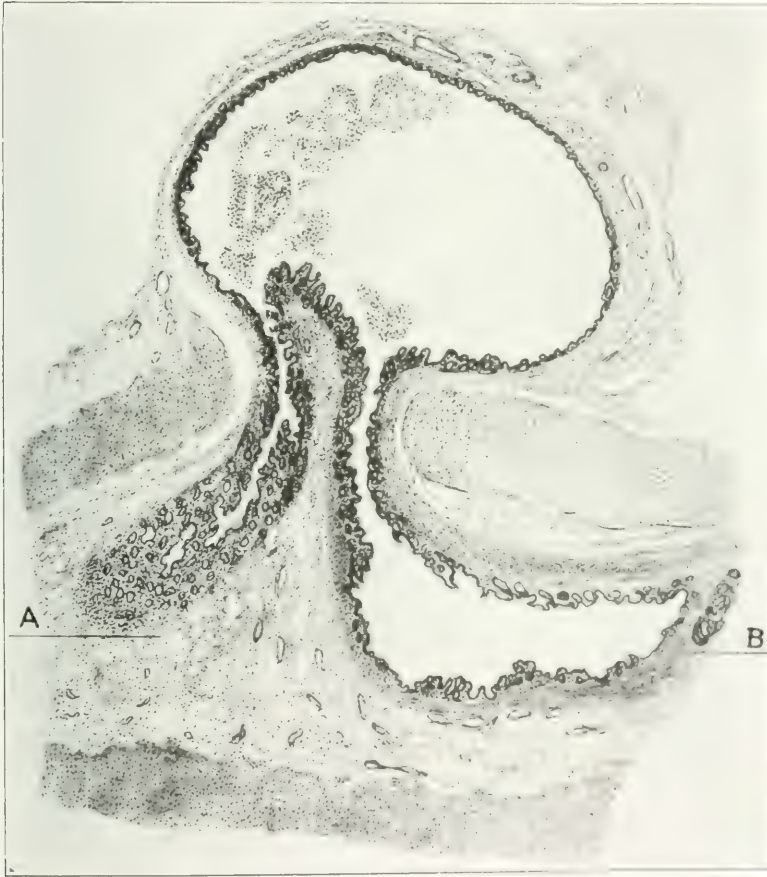


Fig. 3 (Case 2).—Appearance of microscopic section of diverticulum *A* shown in Figure 2: diversion of lumen surrounded by mucosa and submucosa through defect in muscular coats. The section is through a plane which shows the afferent and efferent sections of the lumen passing through the vascular defect, but does not show its continuity toward the cecum at *A*, nor toward the tip at *B*. This continuity is apparent in Figure 2.

there was a defect in the muscularis, and through this, mucous membrane extended to a point almost opposite the external coat. Here it ceased and the rest of the cavity was lined with granulation tissue and filled with a mass of leukocytes mixed with mucus and mononuclear cells (Fig. 4).

The condition in the tip suggested that a mucocele was probably in the course of formation in the distal isolated portion with a diverticulum at its tip. An infection involved the tip, causing a perforation of the diverticulum, which had resulted in abscess formation in the mesentery. The central portion had probably been involved secondarily in the acute inflammatory reaction, causing an empyema involving this portion and its extension into the proximal diverticulum. The small proximal portion attached to the base had practically escaped involvement at this stage of the infection.

Case 1.— (Name) L. W., a colored woman, aged 20, single, an American, who was doing maid service, had suffered pain in the right lower quadrant for the past two weeks, which had grown steadily worse and was increased by urination. There was no nausea, but she had vomited twice. Two similar attacks had occurred, one and two and one-half years ago, with fever which lasted from four to six weeks. In the past, she had four attacks of pain, swelling and redness of the left ankle and shoulder. She was usually constipated. Promiscuous intercourse was admitted.

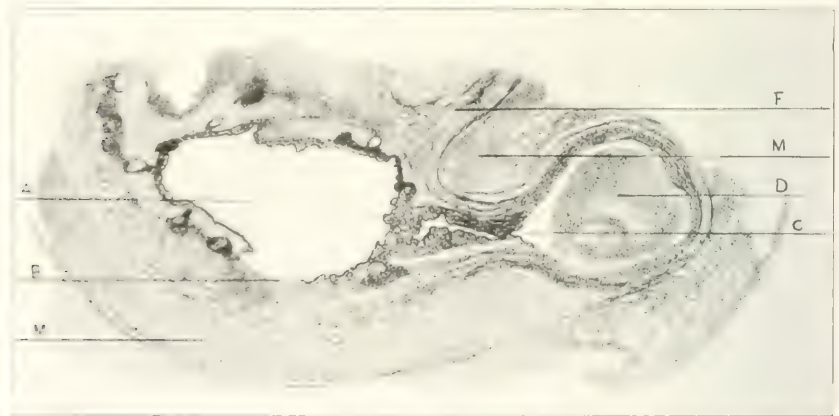


Fig. 4 (Case 2).—Drawing of microscopic slide of section made through tip of appendix at *E* in Figure 2, but at a deeper plane. The lumen of the appendix is shown at *A*, surrounded by inflamed mucosa which has been destroyed at *B*. At *C* is the opening of a mucous membrane lined tract which leads through a defect in the muscular coats *MM*, into an extra muscular cavity *D*, lined with granulation tissue and filled with mucus and pus. At *F* is a connective tissue filled vascular defect passing from the mesenteriolum through the muscular coats to the submucosa.

Examination.—There was marked tenderness low down in the right lower quadrant and slight tenderness in the left lower quadrant. The cervix was large, soft and irregular. There was intense pain when the cervix was moved. There was a tender mass in the right fornix and slight tenderness in the left fornix. The patient was observed in the hospital for eleven days, during which time she improved greatly. The temperature ranged from 101.4 to 98 F. The white blood cells numbered 8,100; polymorphonuclears were 81 per cent.; hemoglobin, 70; the red blood cells numbered 4,600,000. The Wassermann reaction was negative.

Operation (Dr. Joelson, supervised by Dr. J. Greenough).—March 13, 1922: Right salpingo-oophorectomy, left salpingectomy, myomectomy of small uterine fibromyoma and appendectomy were performed. The appendix was retrocecal and entirely retroperitoneal. Uneventful recovery ensued. May 13, 1922, the wounds were fully healed, and the patient felt relieved of symptoms.

Gross Examination.—The specimen was an appendix 6 cm. long and varying from 5 to 8 mm. in diameter. The surface was dull and roughened. The superficial vessels were injected. There were several small firm white nodules on the mesenteric and antimesenteric borders, averaging about 2 mm. in diameter. On the mesenteric border near the tip, there was a much larger one, projecting 4 mm. from the surface and measuring 5 mm. in diameter. On longitudinal section, the lumen of the appendix was found to be patent to within 7 mm. of the tip; from 3 to 4 mm. in diameter, and filled with inspissated fecal material. The wall of the appendix averaged 2 mm. in thickness, of which the muscularis occupied 1 mm. One fibrous band was seen passing through the muscularis in the mesenteric border, which was 0.8 mm. in diameter. The terminal 7 mm. of the appendix seemed to show first an obliteration of the mucosa and its replacement by fibrous tissue; beyond this the lumen was a mere potential space surrounded by a small amount of mucous membrane. It seemed to pass out into the large nodule projecting from the mesenteric border. (A more detailed description of this appendix cannot be given for it was unfortunately mislaid after this preliminary examination had been made). With the appendix were a fibromyoma of the uterus, two chronically inflamed tubes and a cystic ovary.

Microscopic Examination.—Sections from the tip of the appendix revealed a diverticulum formed by the extension of the submucosa and mucosa through a defect in the muscular layers. On one side of the diverticulum, a slender strand of the inner circular muscle had been carried through the gap with the submucosa and extended almost to the highest portion of the dome of the diverticulum. There were two distinct lumina in the diverticulum, lying side by side as it passed through the muscularis, each lined with mucosa and submucosa, which join in the extramuscular sac. A good sized vein lay alongside the neck of the diverticulum as it passed through the muscularis. A section taken from one of the smaller nodules along the mesenteric border described in the gross presented a mass composed of connective tissue surrounding a number of relatively large thick walled veins passing through a gap in the muscularis and widening out to form a thicker rounded mass outside the muscularis, in this way simulating a diverticulum, although no mucous membrane appeared in it. (This is an example of the false diverticulum described by Seelig²⁵). None of the sections presented any signs of acute inflammation.

CASE 4.—History.—E. W., man, aged 54, a widower, American, had suffered for thirty-six hours from generalized pain in the abdomen and vomiting. He had had no previous similar attacks but had had vague gastric disturbances and cramps occasionally in the past. There were tenderness and muscular spasm about the umbilicus and in the mesial portions of both lower quadrants. The temperature was 100.6 F. The white blood cells numbered 21,000; the polymorphonuclears were 93 per cent.

Operation (Dr. Greenough).—Jan. 27, 1922: Appendectomy with drainage was carried out. The appendix lay behind the ileocolic junction in a region

25. Seelig: False Diverticula of the Vermiform Appendix, *Ann. Surg.* **44**: 78, 1906.

of localized peritonitis. A stormy postoperative course was attended by a pulmonary embolus with infarction of the lung. June 6, 1922, there was bulging of the abdominal wound, but the condition was otherwise good.

Gross Description. The specimen was 4 cm. in length, 1.3 cm. in diameter near the base and 1 cm. in diameter at the tip. It was reddened and edematous throughout, but more markedly so in the distal half, which was covered with a greenish-yellow fibrinous exudate. The mesenterium was also swollen and edematous, with a broad attachment. It was covered with a fibrinous exudate throughout its length. On longitudinal section, it could be seen that the thickening in the proximal half was due to a tremendous thickening of the submucosa. The muscular coat was 2 mm. thick. Along the mesenteric border, there were eight vascular defects from 1 to 1.5 mm. in thickness, passing through it at right angles to the lumen. On the antimesenteric border, the vascular defects were barely visible. The lumen for a distance of 2.3 cm. was small but patent and passed with slight deviations nearly through the center of the appendix; then it made a right angled turn and, accompanied by the mucosa and submucosa, passed through the muscular coat to form a dilated sac



Fig. 5 (Case 4).—Appearance of acutely inflamed appendix from a man of 54, who had had no previous attacks. At the left is the external appearance of the appendix, with the thickened mass of the mesentery above, with fibrin adherent to it. To the right is a longitudinal section showing the single diverticulum in the mesenteric border with complete diversion of the appendix lumen into it. The thick muscular coats appear as a broad dark band, interrupted along the mesenteric border by the diverticulum and by seven sharply contrasted connective tissue filled vascular defects.

5 mm. in diameter between the leaves of the mesenterium. It then proceeded directly back toward the center of the appendix, paralleling its former course outward, and passing through the same muscular defect. Having reached the center of the appendix, it proceeded on its course to the tip. The muscular defect through which the two arms of the lumen passed measured 4.5 mm. in width. We thus had a complete diversion of the lumen through the muscularis into the mesenterium. At one point, the mucosa lining the diverticulum was defective, indicating a pin point perforation into the mesentery (Fig. 5).

Microscopic Examination.—Longitudinal sections revealed that the diverticulum in the mesentery had a lumen 5 mm. in diameter, lined with intact mucosa surrounded by submucosa and the thickened edematous, inflamed mesentery. Only one of the mucosal tubes connecting it with the site of the original appendix lumen was shown in these slides. This was also lined with

intact mucosa as it passed through the broad defect in the muscularis. Several other broad defects in the muscularis were seen, through which passed blood and lymphatic vessels and dense connective tissue. Surprisingly little evidence of the acute inflammatory reaction appeared in the section except in the form of a fibrinopurulent exudate on the serosa and fibroblastic reaction in the mesentery, together with a moderate edema and dilation of lymphatic vessels (Fig. 6).

CASE 5.—*History*.—J. F. D., man, aged 21, single, American, a clerk, suffered sudden sharp cramplike pains in the abdomen which were not relieved by any measures taken. The bowels moved, and he vomited once. He had had six similar attacks during the past year. He was usually constipated. The tempera-

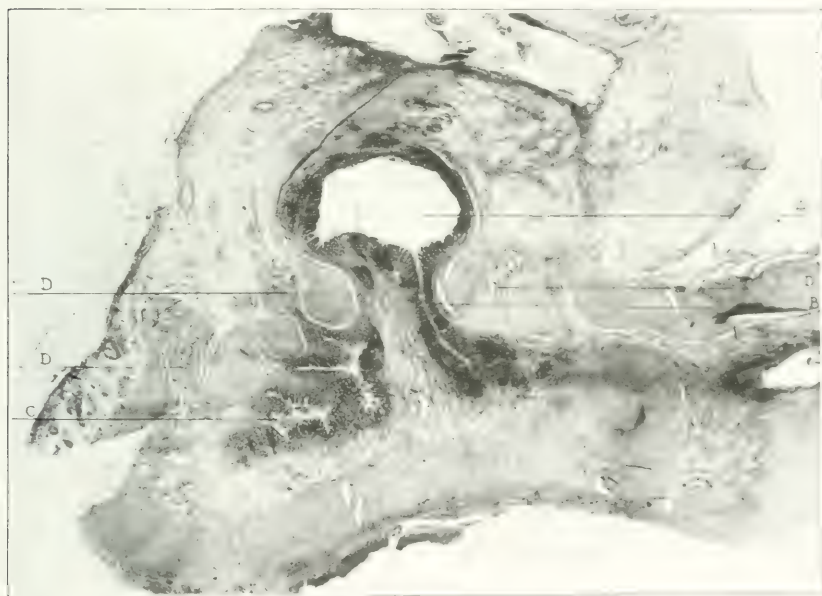


Fig. 6 (Case 4).—Photomicrograph of the appendix shown in Figure 5. The diverticulum lined with mucosa and submucosa in the mesenteric fat is shown at *A*. The afferent portion of the lumen leading from the cecal end of the appendix to the diverticulum sac is shown at *B*. The continuity of the diverticulum with the lumen of the appendix at the tip *C* is not shown in this section but is clear in Figure 5. *DDD* are four of the broad defects in the mesenteric border of the muscularis filled with blood vessels and connective tissue. The ball-like expansions of these outside the muscular coats (so-called false diverticula) are well shown.

ture was 100.6 F. The white blood cells numbered 17,600; polymorphonuclears, 90 per cent. Tenderness was noted on both sides of the midline below the umbilicus. There was rectal tenderness anteriorly, and marked distention of the colon.

Operation (Dr. H. A. Murray, supervised by Dr. W. G. Penfield).—Jan. 9, 1922: The appendix was retrocecal, apparently perforated near the tip, swollen, reddened, and covered with fibrin. A quantity of free, gray purulent

fluid was found in the peritoneum, which grew *B. acidilactici*. Appendectomy was performed, with drainage. The wound healed slowly, but convalescence was otherwise smooth.

July 18, 1922. The scar had a slight tendency to bulge; otherwise the patient was well.

Specimen examined.—The specimen was an appendix about 5 cm. long and 0.8 cm. in diameter. It was slightly curved, reddened and edematous, and the distal half was dusky red and covered with a thick, flaky fibrinous exudate. The mesentery was thickened and attached along the convex border. No diverticula were visible externally, nor was there external evidence of perforation.

On longitudinal section of the organ, it was apparent that at the base for a distance of 5 mm. the lumen of the appendix was completely occluded and replaced by fibrous tissue. Distal to this the lumen was widely dilated and lined with a smooth layer of mucous membrane. It contained cloudy fluid. It was at once apparent that there were three complete diverticula along the mesenteric border in the distal half. Two of these measured about 4 mm. in diameter and consisted apparently of protrusions of mucosa and submucosa

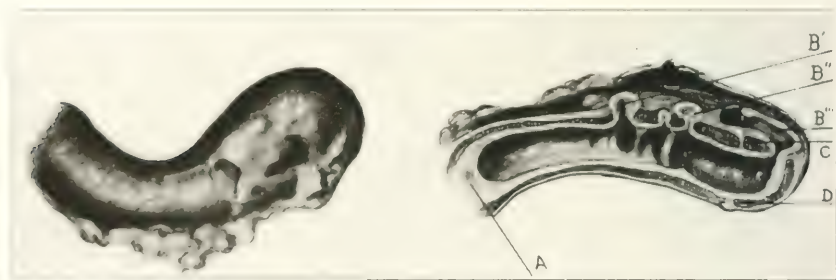


Fig. 7 (Case 5).—Appearance of the acutely inflamed appendix of a man, aged 21, who had had six preceding acute attacks. To the left is the external appearance, showing the tip covered with fibrin and the mesenterium attached along the convex border; to the right a longitudinal section, showing complete obliteration of the lumen at the base, *A*, beyond which it is widely dilated. *B'*, *B''* and *B'''* are three diverticula in the mesenteric border. *C* is a muscular defect in the mesenteric border, and *D*, a muscular defect in the antimesenteric border. Between *B'* and *B''* is what appears to be an incomplete diverticulum. This is incorrectly drawn, as it is a defect similar to *D*.

through defects in the muscularis, which were about 2 mm. in diameter. The most distal diverticulum near the tip was much larger when it reached the mesentery, spreading out over an area nearly 1 cm. in length. It was filled with semigelatinous, mucoid material and there was a perforation through one end into the mesenteric fat. It was noticeable that there were, in addition to the complete diverticula, two defects in the muscularis along the mesenteric border and one along the antimesenteric border, all of which were filled with dense, white connective tissue. The defect on the antimesenteric border was capped with a small ball of dense white tissue in the subserosa. No lumen or mucosa appeared to be present in these three areas. The muscularis measured about 2 mm. in thickness. The broadest point was 2.2 mm. in thickness. The connective tissue filled defects averaged 0.5 mm. in diameter (Fig. 7).

Microscopic Examination.—A section taken near the tip revealed that the largest diverticulum was a protrusion of submucosa, muscularis mucosae and mucosa through a large defect in the muscularis, into the tissue between the leaves of the mesentery. It had spread out considerably in this situation and at its proximal end had a defect in its lining mucous membrane which communicated directly with a mass of mucus lying free in the tissues. This mucus was mixed with round cells and leukocytes. In the surrounding tissues, there was edema, congestion of vessels and cellular infiltration. On the serous surface was adherent an exudate of fibrin and leukocytes (Fig. 8). The other two diverticula were of the usual type. There were also defects in the mesenteric border of the muscularis, filled with connective tissue which surrounded thick walled veins. The lack of signs of inflammatory reaction in the appendix itself made one suspect that the infection started possibly in the mucocoele which came from the diverticulum at the tip of the appendix.

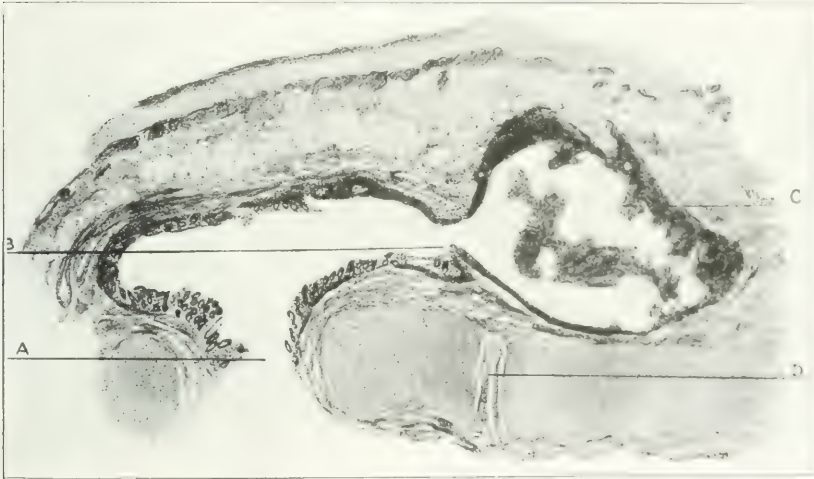


Fig. 8 (Case 5).—Drawing made from the microscopic section of diverticulum B", Figure 7. At A is shown the neck of the diverticulum leading to the extra muscular cavity which is lined with mucous membrane except at B, where it stops at the small opening shown in the illustration. This leads into an accessory cavity C, which is lined with the connective tissue of the mesentery and contains mucus and leukocytes. The mucous membrane lining the lumen of the appendix was torn away in making the section. Here, we have a diverticulum with an infected mucocoele leading off from it. D is a vascular defect.

CASE 6.—*History.*—M. F. C., woman, aged 28, single, American, a book-keeper, came to the hospital to have the appendix removed because of a recent acute attack of appendicitis.

Examination.—On admission, tenderness was elicited on deep palpation in the right lower quadrant. All other signs were negative. The temperature was 99 F. The white blood cells numbered 7,100; polymorphonuclears, 66 per cent.

Operation (Dr. F. B. St. John).—July 23, 1921: Appendectomy was performed. The appendix was found in the pelvis adherent to the surrounding

structures by recently formed soft adhesions. Three nodules were noted along the antimesenteric border and one at the tip. The patient made a good recovery.

Gross Examination.—The specimen measured 6.5 cm. in length and 1 cm. in diameter in the distal half. A large mass of mesenteric fat was attached distally. It was pink and smooth, except in a few scattered areas from which adhesions had been torn. At the tip was a firm rounded pale mass, 7 mm. in diameter. Three similar rounded projections, smaller in size, were seen on the antimesenteric border in the distal half. On longitudinal section, it was seen that the appendix was somewhat irregularly curved, with its concavity toward the mesentery. The lumen appeared to be patent throughout, varying from 2 to 3 mm. in diameter. White lines representing vascular defects filled with connective tissue could be seen in both the mesenteric and the antimesenteric

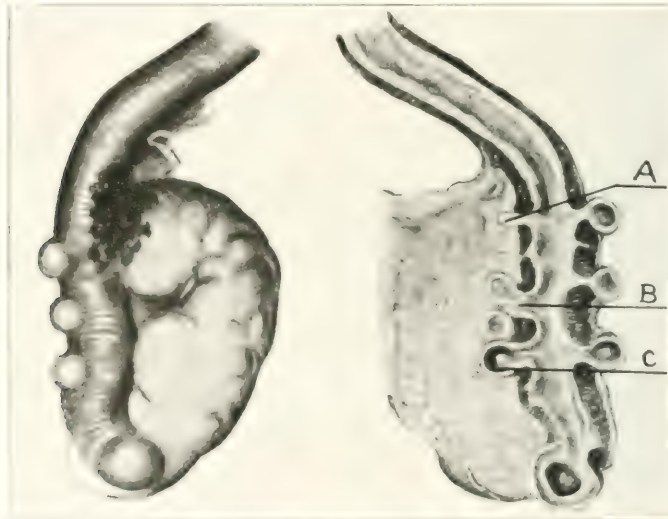


Fig. 9 (Case 6).—Appearance of appendix removed from a woman of 28, in an interval following an acute attack. To the left is the external appearance of the appendix showing the three nodules on the antimesenteric border, one at the tip and the large mass of fat in the mesenterium; to the right, a longitudinal section showing these four diverticula and three others in the mesenteric border, at A, B and C. It will be noted that the lumen is patent throughout and remains within the muscular coats, although diverticulum B has apparently two cavities. (For an explanation of this, compare the gross description of Case 6.)

borders. The broadest one was in the former, measuring 1 mm. in width. It was at once apparent that there were seven diverticula in the appendix: three in the mesenteric and three in the antimesenteric border, and one at the tip, which was the largest. All of these seemed to be simple protrusions of the mucosa and submucosa through the muscularis, which averaged 2.7 mm. in thickness, except the middle one on the mesenteric side, which was a more complicated affair. There seemed to be a fold or septum of mucosa and submucosa in the neck of the diverticulum as it passed through the muscularis, so that in one half of the cut section it appeared as if there were two lumina;

while in the opposite half there appeared to be only one. Outside the muscularis, the diverticulum appeared to have two distinct mucosa lined cavities (Fig. 9). This seemed to be an intermediate stage between the usual simple unilateral protrusion of the mucous membrane and the complete deviation of the lumen into the diverticulum sac, illustrated in the first four cases.

Microscopic Examination.—Longitudinal sections of the appendix taken through the middle revealed three of the diverticula, two on the mesenteric and one on the antimesenteric border. It revealed the tremendously thick mus-



Fig. 10 (Case 6).—Appearance of microscopic section of diverticulum, *B*, shown in Figure 9. The section was made from the half of the appendix opposite that illustrated in Figure 9. In this illustration, the lumen, *A*, passes through the muscularis from the proximal portion of the appendix to an extra-muscular cavity, *B*. This, in turn, communicates with a second adjacent cavity, *D* via *C*, and the lumen then passes back within the muscular coats at *E*. *G* indicates a portion of diverticulum *C*, Figure 9. Although the tongue of submucosa, *F*, apparently occludes the lumen, this condition obtains only in this half of the appendix and not in the opposite half, illustrated in Figure 9.

cular coat, which had a minimum amount of connective tissue in it. Two of the diverticula were simple protrusions of mucosa and submucosa through muscular defects. In the other one, the lumen of the appendix appeared to be completely diverted, passing through the muscular defect into two mucosa lined cavities in the mesentery, which were connected by a narrow passage;

and then passing back again through the muscular defect. These bulbous enlargements were filled with cellular and amorphous debris. In the surrounding fat, there were a few round cells and leukocytes. There was no evidence of acute inflammation (Fig. 10). In places where vascular defects without diverticula passed through the muscularis, the density of the connective tissue surrounding the veins and lymphatics was demonstrated. In one instance, a rounded mass of this dense connective tissue with a mass of tortuous vessels included in it could be seen capping the muscular defect. This reached a diameter of 4 mm. and was an example of the false diverticulum described by Seelig.²⁵ The serosa was thickened and edematous, and presented many dilated capillaries and lymphatics.

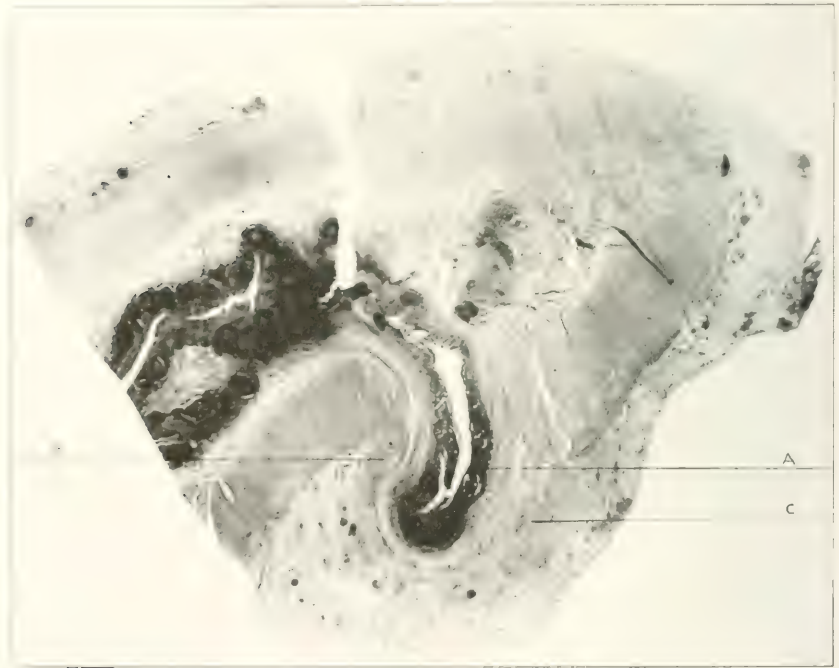


Fig. 11 (Case 7).—Photomicrograph of appendix from a man of 20, removed during an acute attack, with a history of four or five preceding attacks. The section shows the tip of the appendix with a diverticulum, *A*, lined with mucosa passing through a defect in the muscularis. At *B* and *C* can be seen fragmented smooth muscle bundles, which have apparently been carried out for a short distance with the protrusion of the mucosa.

CASE 7.—History.—J. R., man, aged 20, single, American, a farmer, had had pain and soreness in the right lower quadrant for two days. The bowels had not moved for two days. Four or five mild attacks of similar nature had occurred in the past six months. The patient was not usually constipated. There was tenderness in the right abdomen, most marked in the right lower quadrant, with rigidity. There was rectal tenderness high on the right. The temperature was 102 F. The white blood cells numbered 16,000; polymorphonuclears, 85 per cent.

Operation (Dr. Jameson).—April 18, 1915: Appendectomy with drainage. was performed. The cecum was undescended and of the infantile type. The appendix was retrocecal, and an abscess surrounded the tip, which was up under the liver. There was cloudy fluid in the pelvis. The patient made a good recovery. When last seen, twenty-one months after operation, he was perfectly well.

Gross Examination.—(As the specimen has been lost, the following is a copy of the examination made in 1915.) The specimen was 8 cm. in length. It was sharply angulated at the junction of the proximal 3 cm. with the distal 5 cm. The proximal portion was 1 cm. in diameter and, after making the right-angled turn, it disappeared into a mass of edematous infiltrated fat. In the distal portion, the wall was edematous and infiltrated. The mucosa appeared gangrenous, the lumen was patent but was filled with purulent and fecal material; 1 cm. from the tip, there was a diverticulum of the lumen into the surrounding fat. It projected for a distance of 5 mm. and was somewhat bulbous, the broadest part measuring 5 mm. in diameter. The muscularis averaged about 2 mm. in thickness. As the appendix had not apparently been cut in a plane passing through the mesenteric and antimesenteric borders, no vascular defects could be seen.

Microscopic Examination.—Section made through the tip of the appendix revealed that the mucous membrane in this portion was intact and, with the muscularis mucosae and submucosa, passed out through a defect in the muscularis for a short distance, into the surrounding fat. All the coats in this region were edematous and were infiltrated with leukocytes and round cells. This was most marked in the extramuscular fat, where, in addition, all the vessels were engorged and there had been considerable proliferation of fibroblasts. It was interesting to note that a few bundles from both the longitudinal and the circular muscle coats had been carried outward along the side of the diverticulum nearly to its apex (Fig. 11). Aschoff²³ quotes von Brunn²⁶ to the effect that this phenomenon is seen in connection with diverticula which have followed inflammatory damage, and serves to distinguish them from the other type. The evidence is all in favor of this being an example of a diverticulum resulting from a former perforation of the appendix and protrusion of the mucosa, with subsequent repair and regeneration of the mucosa within the extramuscular tissue.

PERFORATED APPENDICES

CASE 8.—*History*.—J. Z., man, aged 31, married, Hungarian, a janitor, had an acute attack of abdominal pain, with constipation, lasting two days, finally localized in the right lower quadrant. There had been no previous attacks. The patient had never been constipated before. There were marked pain and tenderness in the right lower quadrant and right flank. Rectal examination was negative. The temperature was 101.8 F. The white blood cells numbered 22,000; polymorphonuclears, 92 per cent.

Operation (Dr. F. B. St. John).—Jan. 16, 1916: Appendectomy was performed with drainage. The appendix was retrocecal and had ruptured. There was a localized abscess about it, which contained a concretion. Culture of pus showed *B. faecalis alcaligenes* and streptococcus. Two years after operation the patient was perfectly well.

26. Von Brunn: Ueber Divertikelbildung bei Appendicitis, Beitr. z. klin. Chir. 46:67. 1905.

Case 7 Perforation.—The specimen was 4 cm. long. The proximal half was swollen, reddened, and covered with a fibrinous exudate. In the antimesenteric border, there was an area of perforation nearly 1 cm. in length. The mucosa in this area appeared to be everted and was covered with a thick, greenish yellow exudate. The distal half of the appendix was swollen and reddened, but was not nearly so much affected as the proximal part. With the appendix was a fecal concretion which was rounded and firm, and measured about 1 cm. in diameter.



Fig. 12 (Case 8).—Photomicrograph of a cross section through a perforation of an acutely inflamed appendix. The broad defect involving one third of the circumference can be plainly seen, and at *A* and *A'* the extent of the eversion of the protruded mucous membrane, which at *A'* is practically continuous with the serosa.

Microscopic Description.—The section was made transversely through the perforation. All of the coats were much distended with edema and massively infiltrated with leukocytes. The defect in the lumen was in the antimesenteric border and occupied about one third of its circumference. The muscularis had retracted so that it occupied only about one half of the circumference of the appendix. The mucosa and submucosa projected out beyond the muscularis and were everted so that on one side the mucosa reached to the serosa, while

on the other side it extended to a point opposite the middle of the muscularis. The mucosa within the appendix was relatively intact, but the protruded portion was denuded of surface epithelium and was represented by edematous granulation tissue, in which the tubular glands appeared. There was no lymphoid tissue in any part of the submucosa (Fig. 12).

CASE 9.—History.—S. A., woman, aged 23, single, Spanish, a dressmaker, had an attack beginning about thirty hours before operation, of nausea, vomiting and generalized abdominal pain, which later became localized in the right lower quadrant. Two years before she had had an attack of pain in the right lower quadrant, accompanied by fever and vomiting which lasted eight days and during which a mass could be felt in the right lower quadrant. She was treated with morphin and ice bags.



Fig. 13 (Case 9).—Appearance of appendix removed from a woman of 23 during an acute attack, with one previous acute attack two years before. The appendix has been divided longitudinally. The appendix has perforated, with protrusion of the entire lumen. The two wire markers have been passed into the separated portions. The entire nodular area surrounding these two wires on the external surface of the appendix is covered with mucous membrane.

Examination.—On examination, at the Presbyterian Hospital, there were rigidity and tenderness over the lower right rectus, extending out into the flank. No masses were felt. The temperature was 99 F. The white blood cells numbered 12,000; polymorphonuclears, 81 per cent.

Operation (Dr. J. Greenough).—Aug. 8, 1921: Appendectomy was performed, with drainage. The appendix was buried in dense adhesions and was incorporated in the wall of the cecum, starting posteriorly and curving forward along the lateral aspect. There was an old perforation near the tip, from which the mucosa pouted. No holes could be found in the cecal wall. Pus escaped from

the appendix during removal. Following operation, the patient had a secondary hemorrhage in the wound, suppurating parotid sialadenitis, bed sores on the back and heels, and cecal fistula. Jan. 17, 1922, the cecal fistula was closed by operation. March 22, incision and drainage of a subhepatic abscess was carried out. By Jan. 10, 1922, all wounds had healed; the patient felt well and was gaining weight.

Gross Disposition.—The specimen was 5.5 cm. long and markedly curved throughout its length. It was swollen, reddened, and covered with the shaggy remnants of recently separated adhesions. Near the tip in the antimesenteric border was a rounded, elevated area covered with reddened mucous membrane about 1.3 cm. in diameter and raised 5 mm. above the surface of the appendix. In this, there were two pin point openings, one of which was the mouth of a tract leading toward the tip of the appendix, while the other was the external opening of a tract communicating with the lumen of the appendix toward the base. On longitudinal section of the appendix, these two mucous membrane lined tracts could be seen passing through a defect in the muscularis 6 mm. wide. Thus, there was a complete diversion of the lumen of the appendix into the extra-appendiceal abscess cavity. The muscularis near the tip measured about 1.5 mm. in thickness. Several broad white bands in the mesenteric border of the appendix represented the vascular defects. The broadest of these was 1 mm. wide (Fig. 13).

Microscopic Examination.—We were not successful in getting a section which included both tracts in the same slide. However, they showed the mucosa and submucosa passing outside of and well beyond the muscularis and then turning outward and downward until it met the serous coat at a considerable distance from the point at which it passed through the muscular defect. It was well formed, and, in its extra-appendiceal portion, the cells making up the glands were mostly of the goblet variety. The coats of the appendix were somewhat edematous, but presented only a very moderate infiltration with leukocytes and round cells.

PROTOCOLS OF EXPERIMENTS

Experiment 1.—A young adult female mongrel of the hound type, weight about 25 pounds (11.4 kg.), was operated on, Oct. 27, 1921, under ether anesthesia, the appendix and cecum being delivered into the upper part of a right rectus incision. The appendix had a separate mesentery and, except for the tip, was bound down closely to the cecum. It emptied easily into the cecum and refilled almost immediately as soon as the pressure was removed. An area 6 by 8 mm. near the tip was denuded of serosa, subserosa and muscularis by sharp dissection with the knife. At once, the submucosa and mucosa bulged through the defect, forming a dome shaped swelling 4 mm. in height. At the same time, it was noted that the appendix contracted both in diameter and in length, and its wall became very hard. After some seconds, this muscular spasm was relaxed, and, coincidentally with the softening of the appendix wall and the increase in its dimensions, the diverticulum appeared slightly less prominent and its walls slightly less distended. It never disappeared. A ligature, together with an attached piece of omentum, was now tied about the middle of the appendix, passing through a hole in the mesenterium; this constricted the appendix considerably, and it was hoped that, with the formation of scar tissue, a permanent obstruction would be obtained. The abdominal wound was then closed.

The dog, which had been suffering before from distemper, died of that disease, Nov. 18, 1921, twenty-two days after the operation. At necropsy, a

moderate number of adhesions of omentum to the appendix were found. The terminal ileum, cecum, ascending colon and appendix were removed from the body en masse and distended with liquor formaldehydi (formalin) before being studied.

Gross Examination.—The diverticulum was now about 8 mm. in diameter and passed through a muscular defect 5 mm. in diameter. It was, therefore, slightly larger than before. Where the omentum and silk ligature were tied

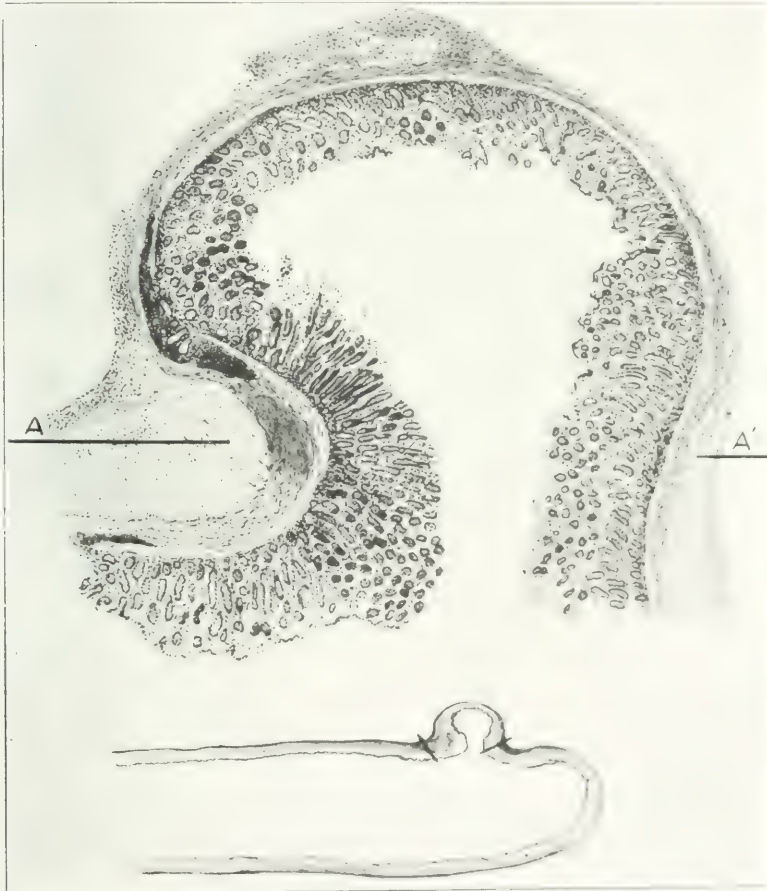


Fig. 14 (Experiment 1). Appearance of distal portion of dog's appendix showing experimentally produced diverticulum twenty-two days after the muscular defect was made. Above is a drawing made from a microscopic section of the area included between the heavy lines in the sketch. It shows at *A* and *A'* the ends of muscle coats with the protruding mucosa and submucosa passing out to form an extra muscular pouch. Attached to the apex of the diverticulum is a torn adhesion.

about the appendix, the lumen was decreased to one half in its diameter, but there was no obstruction.

Microscopic Examination.—A section through this diverticulum was identical with that of "acquired" diverticula in the human appendix. It showed

removal of the muscularis mucosae and submucosa through a muscular defect. Attached to the exposed submucosa was some adherent omentum (Fig. 14).

Experiment 1.—A small male mongrel was operated on Dec. 30, 1921, under ether anesthesia, the technic being a repetition of that employed in Experiment 1. In this case, two defects were made: one, 5 mm. square, by excision of muscular coats, the other, by a simple incision 1 cm. long down to the submucosa. In this case, there was a bulging of the submucosa and mucosa through the defects when the appendix contracted, but it was not marked and almost disappeared with relaxation. A thick doubled silk ligature was tied very tightly about the middle of the appendix, so that the lumen was obstructed.

The dog underwent another experiment performed on his spleen during the same operation, and died two hours later, with shock and mesenteric thrombosis. At necropsy, the appendix was found covered with fibrinous exudate and a small amount of blood. It was soft and flaccid, and, although there was a slight bulge of mucosa and submucosa through the defect, there was no true protrusion forming a sac as in Experiment 1.

Microscopic Examination.—Section showed that the muscularis had been completely removed and that the mucosa bulged through to the level of the surrounding serosa.

Experiment 2.—A young adult female mongrel terrier was operated on, March 20, 1922, under ether anesthesia, the appendix and cecum being mobilized and the appendiceal-cecal junction carefully freed, care being taken to injure as few as possible of the large vessels in the mesentery. After crushing with clamps, the base of the appendix was divided; phenol was applied to the stump, and it was inverted into the cecum and buried by suture. The distal divided end was first opened, so that a small piece of cork about 8 mm. in diameter could be inserted into it; and then phenol was applied, and it was inverted and buried by suture. There was some soiling by appendiceal contents during this stage of the operation. A defect 5 mm. square was made in the wall of the appendix over the cork, exposing the submucosa. At once, the appendix contracted, and the mucosa and submucosa protruded through the defect, forming a small dome-shaped swelling about 2 mm. high. This persisted. The wound was then closed. This operation produced a completely segregated appendix with a foreign body in it and a diverticulum.

The dog developed distemper, and died April 10, twenty-one days after operation.

Necropsy (April 11, 1922, twenty-seven hours after death).—There was a suppurative tracheitis, bronchitis and beginning bronchopneumonia. Considerable postmortem discoloration was noted in the peritoneal cavity. The region of the appendix was completely covered with firmly adherent omentum. When this was separated, the appendix was found lying just as at operation. The diverticulum was well defined and appeared as before. The cork was now in the lumen, but slightly nearer the tip. There was no distention of the segregated appendix. The intestines were empty except for a minimal amount of fecal material in the large intestine. The duodenum, with the pancreas in its mesentery, had become intimately adherent to the site of operation. Fluid could be passed only with difficulty through the cecum. After distention with liquor formaldehydi, the whole area was removed for study. When the specimens were examined, it was found that the appendix had perforated and there was a closed

abscess cavity outside the base, the walls of which were formed by the cecum, duodenum and pancreas. The cork lay just beyond the site of the diverticulum. The lumen of the appendix was not dilated, averaging 3 to 5 mm. in diameter. It contained some cloudy fluid mixed with débris. The diverticulum measured 1 cm. where it passed through the muscularis, and it projected for a distance of 3 mm. above the surrounding serous surface. The cecum, where the wall had been inverted, was sharply angulated and its lumen reduced to a semilunar slit, 6 mm. from horn to horn and 0.5 mm. at its broadest point. There was fecal material, however, on both sides of this narrowed area.

Microscopic Examination.—Sections of the diverticulum revealed a bulging of submucosa, muscularis mucosae and mucosa through a defect in the muscularis. None of the muscularis remained over the denuded submucosal surface. Sections made through the point of perforation of the appendix and the abscess cavity revealed that the walls of the latter were made up of adherent duodenum and cecum, both of which were relatively normal, except that the serosal surfaces were covered with a necrotic layer where they bordered the abscess cavity, and there was a portion of pancreas which presented extensive degenerative and fibrotic changes. The abscess cavity contained many mononuclear cells and a few leukocytes, together with much amorphous débris.

Experiment 4.—A dog which was about to be killed was selected and anesthetised with ether. A defect 4 mm. square was made in the appendix near its tip, down to the submucosa. The submucosa and mucosa at once protruded from 2 to 3 mm. through the defect, and at the same time the strong muscular contractions which involved the entire organ made it hard, shorter and of smaller diameter. It was observed for some minutes, during which time the muscular contractions were relaxed and then it contracted once more. During the period of relaxation, the diverticulum seemed to become somewhat flaccid, although its total projection was not less.

A metal syringe was now passed through a slit in the cecum up into the appendix and a silk ligature tied about the appendix base over the nozzle, in an attempt to make the appendix a closed cavity. Water was then injected. At first, the lumen of the appendix filled with water, which passed into the diverticulum, and it stood out as a firm, smooth hemisphere above the surrounding serosa. As more and more water was injected, the diameter of the appendix continued to grow greater, and as it did so, the projection of the diverticulum above the surrounding serosa grew steadily less, until there was no longer any projection at all, although the muscular defect had practically doubled in diameter. With all the force which could be exerted through the syringe, an attempt was made to burst the appendix, but this did not occur, as the increased tension caused the ligature tied about the base of the appendix to cut through so that it leaked at this point. The attempt was repeated several times, with the same result. The dog was then killed.

Experiment 5.—A dog was killed with chloroform, and the peritoneal cavity was opened and left exposed to the air. From time to time, bits of serosa and muscularis were excised from the wall of both the large and the small intestine. Each time, there was the usual muscular contraction, resulting in the narrowing and shortening of the segment injured and a protrusion of the submucosa and mucosa through the defect. As time passed, the force of the muscular contraction grew more feeble until, about four hours after the death of the animal, there was no longer any response to the injury. The extent of the protrusion through the gap was variable, and seemed to be influenced by the

amount of the contents of the lumen. When a loop was emptied of its contents, however, and a defect then made with the contraction of the muscular tissue there was a protrusion.

When there was no longer any response of the muscular tissue to injury, a defect was made through the muscularis of the appendix, exposing the submucosa; but no protrusion occurred through it. It was possible, by manipulation, to force some of the loose flaccid mucosa and submucosa through the gap, and when manipulation ceased, a fold remained projecting very slightly through the gap. When this procedure was repeated in the intestine, the results varied; if the loop selected was not empty, a protrusion followed the defect; if it was empty, no protrusion occurred.

A syringe was then inserted through the cecum into the appendix and tied into place. When it was distended through this, as in Experiment 4, the first result was the protrusion of the flaccid mucosa and submucosa, forming a smoothly rounded hemisphere above the surrounding serosa. With the tension increased, the sequence of events was exactly the same as in Experiment 4. The diameter and length of the appendix slowly increased, while the projection of the diverticulum grew steadily less, until it ceased entirely. Attempts to burst it succeeded only in causing leaks where the ligature was tied about the base of the appendix.

CASE REPORT.—C. D., aged 33, married, American, a housewife, during the previous four months had had three attacks of acute, cramplike pain, starting in the epigastrium, and radiating to the lower quadrant and around both sides to the back, with vomiting. A bowel movement gave relief. The attacks lasted about one day, and tenderness persisted in the right lateral quadrant after attacks. On examination, there was tenderness in the right lower quadrant and right fornix. The white blood cells numbered 10,600; polymorphonuclears, 70 per cent. The temperature was 98.8 F. Aug. 25, 1922, three days after admission appendectomy was performed by Dr. Freeman, Jr., supervised by Dr. W. B. Parsons. The appendix was retrocecal and twisted on itself. The proximal two thirds was covered by a vascular veil.

This appendix was taken immediately after removal and laid on a cork mat beside a millimeter scale. A defect 6 by 6 mm. was made through the muscularis of the antimesenteric border near the tip. When first laid out, the length of the appendix was 7.2 cm. and the average diameter 6.5 mm. At the end of fifteen minutes, it measured in length 6 cm. and in diameter 7.5 mm. At the end of one hour, it measured in length 5.5 cm. and in diameter 7.5 mm. During the first few minutes, the submucosa and mucosa pouted through the muscular defect until they projected 1 mm. beyond the serosa. They remained in this position without change during the rest of the hour of observation.

The appendix was then distended with fluid through the cut end. It passed freely to the tip and, with the inflow of fluid, the appendix increased in length up to 7 cm., and the projection of submucosa and mucosa through the defect returned within the muscular wall, so that the diverticulum was ironed out and disappeared.

The appendix was then fixed in liquor formaldehydi. On longitudinal section, the muscularis was found to vary from 0.4 to 0.9 mm. in thickness. Microscopic sections revealed some scarring of the inner muscular coat and round cell infiltration of all the coats.

The patient made a good recovery, and the appendix was believed to have been the seat of the trouble.

SUMMARY OF CASES OF DIVERTICULA OF APPENDIX

Case	Sex	Age	Previous Attacks of Acute Appendicitis	Habitually Constipated	Removed During Acute Attack	Diverticulum Involved in Acute Inflammation	Duration of Acute Symptoms	Position of Appendix	Lumen of Appendix Obstructed Between Diverticulum and Cecum		Diameter of Diverticula, Min.	Diverticula						Associated Condition				
									By Angulation or Twisting	By Obliteration of Lumen and Mucosa		Number	Along Mesenteric Border	Along Antimesenteric Border	At Tip	Transverse	Vessels Alongside Neck of Diverticulum		Width of Broadest Vascular Portion of Mesodivertic Border, Min.	Vasculature Present in Mesodivertic Border	Greatest Thickness of Muscularis, Min.	Whole Length Inverted
1	♂	46	?	?	At the autopsy	Yes	3 days	Pericolic	Yes	No	From 3 to 4	1	0	1	0	Yes	1	No	0	1	1	
2	♂	50	No	No	Yes	Trace	3 days	Left colic	Probably	In one	From 3 to 5	1	0	1	0	Yes	1.2	Yes	1.5	1	1	
3	♀ (red blood)	50	Probably not	Yes	No	Yes	1 day	Retrocecal and retroperitoneal	Possibly (inspissated feces in it)	Yes	5	1	0	0	0	Yes	0.8	No	1	1	1	Salpingitis, cystic ovary, fibromyoma
4	♀	54	No	1	Yes	Yes	1 day	Behind retroperitoneum	No	No	5	1	0	0	0	Yes	1.5	Yes	0	1	1	
5	♂	44	4 attacks	Yes	Yes	Yes	10 weeks	Left colic	No	Yes	From 4 to 10	0	0	0	0	Yes	0.5	Yes	1.2	No	No	
6	♀	58	1	1	No	No	10 weeks	Left colic	No	No	From 3 to 5	1	0	1	0	No	1.0	Yes	0.5	No	No	
7	♀	50	4 attacks	Yes	Yes	No	3 days	Retrocecal	Yes	No	5	1	0	0	1	No	1	1	1	1	1	

* In all the columns 1 = somewhat marked, 2 = moderate, 3 = marked.

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NON-SPECIFIC GRANULOMATA OF THE INTESTINE.

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OUR purpose in this paper is to describe the pathological and some of the clinical features of a malady which, we have reason to believe is not uncommon, and yet, as far as we are aware, is not widely known in this country. Its recognition thus far seems to have been confined to European observers. Its literature, strangely enough, covers but little more than the past decade, is almost entirely casuistic and concerned more with the clinical phases rather than the pathological. Even before this period descriptions of this lesion are by no means uncommon, but under the designation of "hyperplastic tuberculosis of the intestine" or syphilis. With a more rigid histological critique we believe this lesion can be partitioned from the large group of specific intestinal granulomata. Its interest is not entirely morphological. It is important clinically and is a malady which both the clinician and surgeon must consider in dealing with obscure tumors of the abdomen. The cause, with exceptional instances, is thus far unknown.

Case Reports. CASE I.—J. K., male, aged twenty-three years.

Family History. Father died of pneumonia; two sisters and one brother living and have always been well.

Previous History. The patient had measles, whooping cough, scarlet fever and pneumonia as a child. No rheumatism.

Present History. In December, 1917, the patient was first seen by one of us. He had a diarrhea averaging seven to eight move-

* Read before the American Association of Pathologists and Bacteriologists, Washington, May, 1922.

ments a day for the past year. The stools were soft and occasionally tinged with blood; no cramps. He was a thin (112 pounds), pale somewhat anemic boy. There was a short presystolic murmur at the apex. The abdomen was lax, flat; no tenderness or mass. Under diet, etc., treatment and salol he improved so that he had but two or three fairly well formed movements a day. There was steady gain in weight (119 pounds). In May, 1918, he was operated upon for a typical attack of acute suppurative appendicitis from which he made a perfect recovery. In November, 1918, he had pain in the right iliac fossa. The bowels moved three or four times daily. A mass was found in the right iliac fossa, the size of a peach, firm, circumscribed and moderately tender. There was no fever. Weight has come down to 112 pounds. The condition remained practically stationary until February, 18, 1919, when he was operated upon by Dr. Wilensky. The cecum was found to be the seat of a hard firm mass. A resection was done with an end-to-side anastomosis. A fecal fistula persisted and remained open all summer. Bowels continued to move three or four times daily. In October, 1919, he was again operated upon by Dr. Wilensky. The fistula was closed. For the next year the bowels moved two or three times daily. Occasionally he would get attacks of diarrhea with more frequent movements, but without cramps. Such attacks usually lasted all night. In December, 1920, he suffered from an attack of acute intestinal obstruction. Resection of about a foot of ileum; the boy made a good recovery. The blood Wassermann was negative.

After this operation the patient felt well. His bowels moved two or three times daily, once or twice in the morning and once or twice after supper. There are no cramps with these movements. In January, 1922, he had an attack of six hours duration of abdominal pain, generalized and severe, with complete obstruction of the bowels. No vomiting, some fever. General impression, acute intestinal obstruction. Immediate laparotomy; large exudate of yellowish purulent material gathered for greater part on right side and under cover of great omentum and transverse colon; bowels distended; bowel well injected but not thickened and covered with fibrin in places. No local lesion was discovered to account for the peritonitis. Drainage was provided and the abdominal wall closed. A culture of the pus showed no pneumococci. The boy made an uneventful recovery.

Microscopic Description. Colonic Specimen (Fig. 1). The specimen consists of a piece of large gut 14 cm. long; the lumen of the middle half for a distance of 9 cm. is extremely constricted so that it is impossible for even the small finger to pass through. On opening the gut this constriction is found to be due to an extensive infiltrating swelling which begins imperceptibly at the proximal portion of the intestine so that the upper entrance to the structure is funnel

shaped. The swelling becomes gradually thicker as one proceeds downward where it ends almost abruptly by a much thickened smooth and rounded ridge. The mucosa at each end appears perfectly normal; as it approached the thickening the folds become larger and smoother; on the summit the mucosa is almost perfectly smooth. The gut surrounding the strictured portion is tremendously thickened. On section through this portion the thickening involves all the layers: the mucosa, musculature and the mesenteric fat. The thickening is dense, hard and white. The external surface is comparatively smooth where it has been peeled away from the surrounding connective tissue. There are a few hemorrhages into the fatty layer.



FIG. 1.—Ascending colon, Case I, showing tumor constricting gut.

Microscopical Examination. The mucosa shows a classical membranous inflammation. The superficial mucosa is congested and covered by a layer of varying thickness of fresh fibrin which springs from numerous crypts in the mucosa. In extensive areas the mucosa has been destroyed revealing ulcers covered by fresh fibrin beneath which the submucosal lymphatic tissue has been converted into frank granulation tissue. With the low power the entire thickness of the gut appears densely infiltrated. The cells are either heaped together in circumscribed clumps resembling the normal lymphoid structures of the intestine or scattered in lesser or greater densities throughout all the tissues. The clumps as well as the scattered infiltrations lie within the muscular zones causing extensive deformity of the muscle bundles. They are abundant in the fatty and connective tissues external to the muscular

coat as well. With the higher power the infiltrating cells are those of the round- or plasma-cell type. In the more superficial tissues polymorphonuclear leukocytes are abundant, due to the contiguous acute membranous inflammation, but in the deeper tissues these are practically absent. A noteworthy finding is the presence of abundant giant cells. These are usually present within the solid lymphoid gland-like clumps of round cells described above. In some sections they are more abundant than in others and they are present in the deeper portion of the specimen as well as in the superficial. The giant cells are usually very large, oval or irregular in shape and connected with their immediate environment by numerous "pseudopodia." The giant cells contain numerous nuclei irregularly distributed. A rather strange finding is the presence of giant cells in what seems an apparently normal lymph follicle in a portion of contiguous colon that is otherwise entirely normal.

The vessels aside from containing abundant polymorphonuclear leukocytes in the superficial portions, show no change. Sections stained for tubercle bacilli and by Levaditi are negative.



FIG. 2.—Cross-section of the small intestine, Case 1, showing almost obliteration of the lumen by the granulomatous tissue.

Macroscopical Appearance of Resected Small Intestine. (Fig. 2) Specimen consists of a portion of small intestine about 8 inches long; with the exception of a small portion at each end, the gut is extremely thickened and enlarged. The peritoneal surface is much congested and is covered with fresh fibrin. Cross-section shows an immense thickening of all the coats of the gut so that the lumen is merely a bare slit. The infiltration involves the adjacent mesentery, which averages 1 cm. in thickness; the villi are much thickened and in consequence appear much wider and rounded

than normal. The mucosa is deeply congested and the lumen contains a moderate quantity of fresh fibrin which covers the surface of the mucosa. Removal of the fibrin reveals numerous superficial flat ulcerations. The transition of the thickened portion of intestine into the normal is gradual.

Microscopical Examination. The microscopical appearance is practically identical with that of the preceding with one important and notable exception, namely, the presence of a far greater number of giant cells, the majority of which contain a peculiar foreign body. The giant cells are so abundant that on the average three or four are in every low power field. Many are still within the

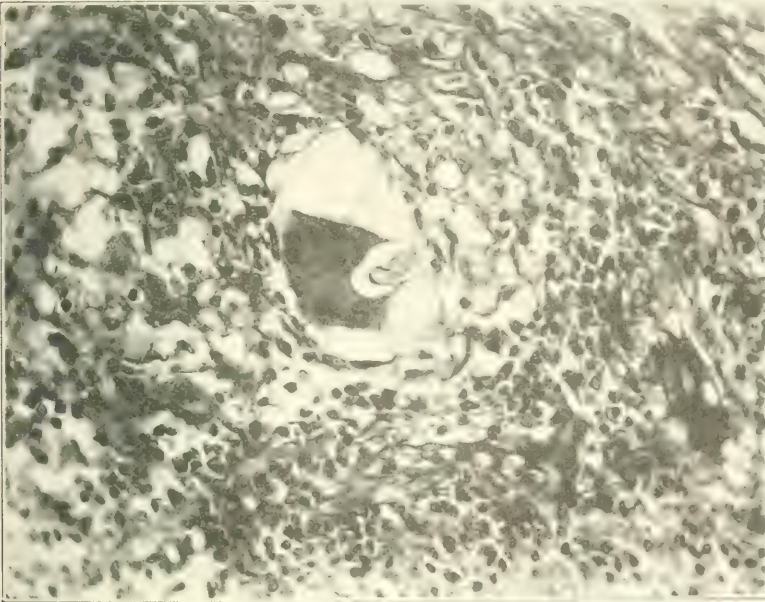


FIG. 3. High power of a giant cell containing foreign body.

clumps of lymphoid-like tissues, but they now show an extremely irregular distribution. They lie imbedded within the muscular fibers surrounded with a sparse collection of round cells. Many are even in the subperitoneal connective tissue coat or in the mesenteric attachment. The giant cells (Fig. 3) are extremely irregular in size, usually round or oval in contour and have a scalloped border from which numerous pseudopodia radiate in with the surrounding round cells. The nuclei are abundant and stain deeply. The nature of the containing foreign body cannot be distinctly made out, because morphologically the thing, even under oil immersion, has no definite structure or outline. As a rule it is round, sometimes oval, sometimes biscuit-shaped. It appears

highly retractile and stains either not at all or pale with hematoxylin. Sometimes it appears coarsely lamellated; at others it consists of irregularly shaped refractile masses; sometimes a giant cell may enclose a simple faintly staining striated curved rod. In one or two the foreign body appears to have a radial arrangement. Whatever the masses may prove to be there is no question but that their structure is so dense as to have been injured by the microtome, because in the vast majority these foreign bodies apparently have been disrupted. It is for this reason that they lack definite structure. Sections stained for tubercle bacilli and by Levaditi are negative.

Summary. A man, aged twenty-three years, suffered from a diarrhea of a year's standing which responds to treatment. He is operated upon for an acute suppurative appendicitis. Six months later a mass in the right iliac fossa appears which is resected and proves to be a granuloma. He remains practically well for two years when an attack of acute intestinal obstruction occurs. At operation about a foot of ileum is resected. The gut is almost completely obstructed by a granulomatous growth extending throughout the length of the gut. Microscopically this growth is characterized by the presence of numerous giant cells surrounding foreign bodies of unknown nature. A year later an acute suppurative peritonitis occurs the origin of which could not be determined at operation. The patient at present suffers from a mild diarrhea, but is otherwise well. Every clinical and microscopical evidence of tuberculosis or syphilis is lacking.

CASE II. (Obtained through the kindness of Dr. Seward Erdman.)—J. K., Russian, aged thirty-three years, operated upon at New York Hospital by Dr. Erdman in April, 1920, when he performed a resection of the cecum and ascending colon with lateral ileo-colic anastomosis. Eight days previous to admission he had suffered from pain in the right lower quadrant with vomiting and constipation. He denied having had any such symptoms previously. His appendix has been removed in the course of an operation for right inguinal hernia in October, 1917, at the New York Hospital, at which time the operator (Dr. Vietor) remarked that the appendix was delivered into the wound with some difficulty and with some trauma to the cecum. The appendix did not appear to be diseased and it certainly was not indurated enough to interfere with the usual technic of invagination of the stump. In April, 1921, Dr. Erdman examined the patient and no masses in the abdomen were palpable. The patient said he felt perfectly well, had gained 20 pounds and was not suffering from any gastric or intestinal symptoms.

Macroscopical Description. (Fig. 4.) Specimen consists of a portion of large intestine 8.5 inches long. The opened bowel

reveals a raised tumor-like projection extending longitudinally at about its middle portion. The mass is situated on the posterior aspect, and measures 2 inches in the vertical diameter and 1.5 inches transversely at its widest portion and is three-quarters of an inch thick at its highest elevation. The mass is egg-shaped. The lower margin is thickened, curved with its convexity downward and overhanging. From here the mass narrows slowly as it courses upward and merges imperceptibly into the mucosa. Laterally the tumor overhangs the adjacent mucosa at its lower portion; above it merges gradually into the surface of the bowel.

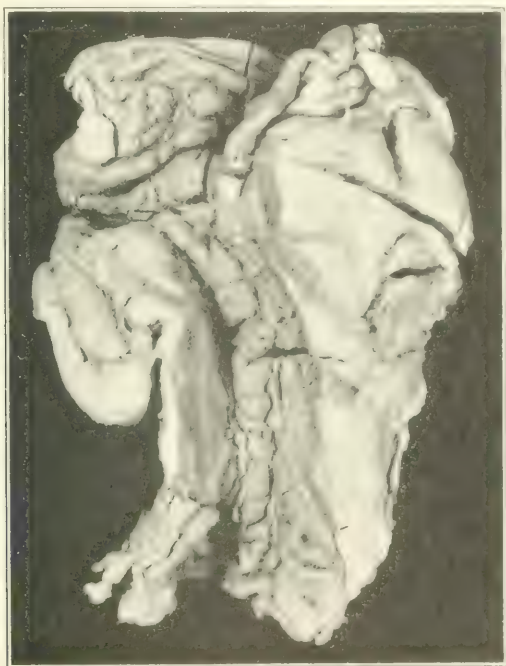


FIG. 4.—Ascending colon from Case II, showing structure of the tumor by the granulomatous infiltration.

At about its middle, there is a flat ulceration with a slightly roughened base, somewhat circular and measuring about 2 cm. in diameter. The surface otherwise is uneven, but the usual Kerckring folds are absent. Section through the mass shows a dense infiltration of all the coats of the intestine for a considerable distance beyond the confines of the mass.

Microscopical Examination. (Fig. 5.) Incidentally this section is representative of all the cases we present. The mucosa appears everywhere intact except at the site of the ulceration. Morphologically no abnormality is visible. The remaining coats of the

cut are densely infiltrated with cells mostly of the round and plasma type. These cells are heaped together in dense but not sharply circumscribed areas so that even grossly the cut section appears as though studded with tubercles. But there is a very great diffuse infiltration in all the tissues especially in the muscular layers so that the muscle bundles are separated, disorganized and deformed. The submucosa and subperitoneal connective tissue coats are much thickened due to an obvious fibroblastic transformation. These layers have all the appearance of young fibrous tissue. The lymphoid structures are intact and reveal nothing abnormal. The bloodvessels are numerous and show some thick-

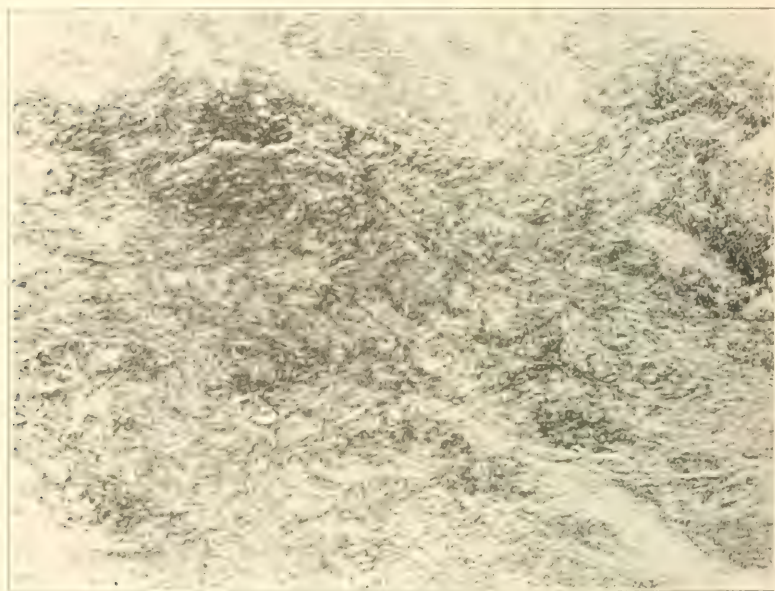


FIG. 5.—High-power section of colon, Case II, showing nature of the granulomatous infiltration.

ening of the media. No giant cells are at all visible. In one section taken from the ulcerated area there is a circumscribed and apparently extensive infiltration with polymorphonuclear cells in the submucosa forming a small abscess. Lymph nodes removed from the mesentery are fairly large and are normal. Sections stained for tubercle bacilli and *Spirocheta pallida* are negative.

Summary. A man, aged thirty-three years, is operated upon for an inguinal hernia at which time an appendectomy is performed. Two and a half years later acute symptoms resembling those of an attack of appendicitis arise. A large mass in the ascending colon is found which proves on microscopical examination to

be a simple chronic granuloma. The patient up to last report is entirely well.

CASE III. L. D., tool maker. Presbyterian Hospital 142738 (Path. No. 26199), admitted July 23, 1919. Five days previously had abdominal pain and vomiting. Appendectomy with drainage by Dr. Langworthy. Toward the end of convalescence the patient complained of pain in right upper quadrant and back. This persisted and is getting worse. Fever of 101° F. since onset.

Physical Examination. There is dullness in right upper quadrant extending to midline. Tenderness in this region extends back to spine. Recent healed appendectomy scar is visible. Stool and Wassermann were negative as well as the urine. No fever.

Readmission. April 24, 1921. Three weeks' complaint of general malaise, chilly sensation, pains in left lumbar region. The patient was told he had "nephritis;" later the physician diagnosed abscess around left kidney. Bowels were costive.

Physical Examination. In the left flank a mass is felt on bimanual examination, tender, smooth, firm, which can be pushed forward and backward. No fever.

Diagnosis. Perinephritic abscess. Roentgen-ray shows a slightly enlarged left kidney, but no tumor of colon.

Operation. May 14, 1921, Dr. Auchincloss. Colectomy for mass just below splenic flexure.

Macroscopical Description. (Fig. 6.) The specimen is a segment of larger intestine, 21 cm. long. It is curved, forming the letter C about a central mass of tissue to which it is densely adherent. This mass is composed of a rolled-up bunch of fat, the center of which is filled with innumerable whitish or reddish-yellow amorphous masses which suggest caseation but are not so soft. The colon is contracted, thick walled and contains fecal material. On section the colon appears normal, except in the distal edge of one segment of the gut where the tumor has encroached to the very edge of the mucosa but apparently has not broken through. The tumor at this point has been much narrowed.

Microscopical Examination. Sections of the mesenteric mass shows a fibroblastic tissue containing many capillaries and densely infiltrated with round and plasma cells and leukocytes. The round cells predominate. In some places the cells are closely massed together which probably accounted for the yellow masses described in the gross. There is little actual necrosis of tissue. Section of one of the lymph glands on the outside of the mass shows a wide dilatation of the lymph sinuses with reticulum in which a few mononuclear cells are caught. Gram stain is negative. Section of the wall of the larger intestine shows a thin but intact mucosa with normal appearing glands and a slightly edematous stroma infiltrated with a few leukocytes and plasma cells. The muscular

coat is edematous and densely infiltrated in many places with round cells. The submucosa is considerably thickened, quite vascular and infiltrated with many polymorphonuclear leukocytes and a few round cells. Serosa covered with thin layer of fibrin.

Diagnosis. Chronic colitis, chronic mesenteric lymphadenitis. A blood Wassermann taken after discharge was negative. A fistula resulted which was closed by Dr. Auchincloss. The patient reported in November, 1921, as being perfectly well.

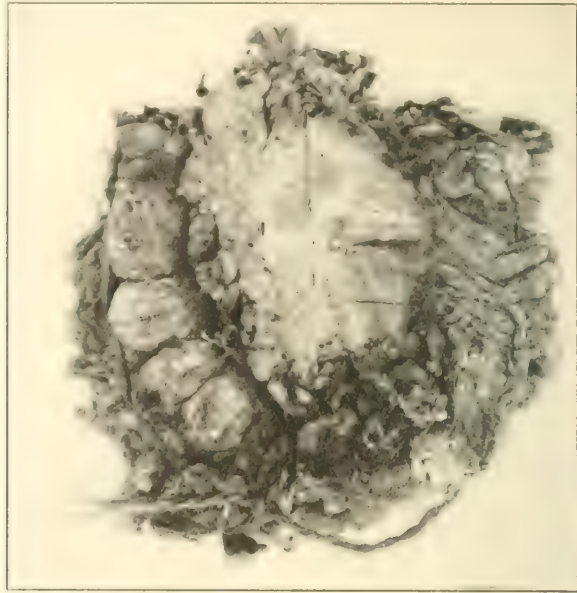


FIG. 6.—Splenic flexure, Case III, showing granuloma of the mesentery infiltrating intestinal wall.

Summary. A man, aged forty-four years, is operated upon for an acute suppurative appendicitis. Appendectomy is performed. After the operation symptoms and signs suggestive of an inflammation in the right side of the abdomen appear which slowly subside. Nearly two years later he presents himself with a mass in the left kidney region which proves upon operation to be a granulomatous mass in the splenic flexure of the colon, the main bulk being in the mesentery but involving the walls of the gut and apparently not breaking into the mucosa. Microscopical examination reveals no evidences of tuberculosis, syphilis or lymphogranulomatosis. The patient up to last reports remains well.

CASE IV.—L. O., aged forty-four years, admitted to Presbyterian Hospital, December 26, 1918. (Presbyterian Hospital 40305 Path. Lab. 22256.) Three weeks ago she was seized with abdom-

inal pains, cramp-like; vomited at onset. There was swelling of the abdomen, most marked in right upper quadrant, which went down considerably after a copious urination. Has had no severe pain since onset.

Physical Examination. In the right upper quadrant of the abdomen is a tender mass, extending to the upper epigastric region. It is round, smooth, somewhat movable and seems to descend on inspiration. This mass seems to be the lower pole of the kidney. Otherwise examination is negative. Wassermann is negative. Feces show no blood. Roentgen-ray shows a filling defect in the ascending colon just below the hepatic flexure.

Operation. January 18, 1919, Dr. Whipple. Colectomy and ileocolostomy. *Macroscopical Description.* The specimen consists of a cecum, appendix and a short portion of the ileum and ascending colon. The serosa of the cecum is smooth, the vessels are slightly dilated. There is a firm irregular nodular mass on the lateral aspect of the ascending colon, 13 cm. from the fundus of the cecum. The appendix is small, 3 by 0.3 cm. The lumen is obliterated. The cecum on section contains feces. The walls appear normal in thickness. The wall of the ascending colon is moderately thickened and the site of the dense mass described above. At one point there is a small nodule 1 by 3 cm. projecting into the lumen of the gut. Section through the larger mass shows a relatively dense tissue having a mottled yellow and white appearance. The gut wall is thickened at this point and the mass is adherent to it. Section through the small mass projecting into the lumen shows it to be closely connected with the main tumor mass at a point in which the yellow substance described above is found in small areas in the gut wall extending as far as the mucosa.

Microscopical Description. All the coats of the intestine are densely infiltrated by a fibroblastic process which varies from a cellular and apparently fresh granulomatous tissue, with many newly-formed blood spaces to a comparatively dense fibrous structure. This new tissue is especially prominent in the submucosa and infiltrates the muscle to such an extent as to cause extensive separation and distortion of the bundles. The predominant cells are of the round type. These cells are heaped together in dense masses in many areas. There is no necrosis and no giant cells are found. The appendix shows complete obliteration of the lumen by fibrous tissue and extensive fibrosis of the muscular coats. The serosa is thickened and infiltrated with round and polymorphonuclear cells.

Diagnosis. Chronic colitis, chronic appendicitis.

Patient recovered and was discharged February 8, 1919. On July 17, 1919 she reported herself well.

Summary. A woman, aged forty-four years, is seized with sudden cramp-like pains in the right side of the abdomen. Upon

admission three weeks later a large mass is noted in the right iliac fossa which proves upon roentgen-ray examination to involve the ascending colon. At operation, the mass is resected. Microscopically it proves to be a simple granuloma. The appendix reveals chronic inflammation. No microscopical evidences of tuberculosis, syphilis or lymphogranulomatosis are noted. Up to last reports the patient remains well.

According to criteria of pathology these 4 cases may be classified as "granulomata of non-specific morphology." All evidences of tuberculosis, syphilis, lymphogranulomatosis (Hodgkin's disease) or new growth are lacking.

Gross Characteristics. All 4 specimens with the exceptions of the small intestine (Case I) resemble one another closely. There is a firm dense unencircumscribed tumor involving all the coats of the large intestine causing stricture of the lumen. There is ulceration in all but 1 (Case III). The ulceration is comparatively superficial and does not penetrate beneath the mucosa. In 3 cases the ascending colon is involved, in the fourth the splenic flexure. The second specimen from the first case is the only one in which the small intestine is involved. It also involved all the coats of the intestine and the encroachment into the mucosa was so great as to cause almost complete obliteration of the lumen. Involving, as it does, almost a complete foot of the small intestine, the lesion, as far as we have been able to investigate, is unique. The infiltration was most prominent on the mucosal aspect of the intestine in 3 cases. In the fourth, the main bulk of the tumor projected into the mesentery.

Microscopical Characteristics. The 5 specimens, again with the exception of the small intestine, reveal a uniformity in microscopical morphology. There is an extensive infiltration of all the coats with cells of the round- or plasma-cell type. It is hard to determine in which layer the infiltration is greatest, but to us the submucous layer seems most extensively involved. There is a widespread fibroblastic transformation varying from a comparatively richly cellular tissue to firm dense fibrous scar. The number of polymorphonuclear leukocytes in our specimens varies considerably. In those with ulceration they are numerous in the neighborhood of the ulcer. In the second case they are congregated in such abundance in the submucosa in one area as to justify the term abscess. In the remaining portions of our specimen these cells are only sparsely scattered. New bloodvessel formation is prominent in all specimens.

Giant cells are absent in all cases except the first. In both specimens from this case their distribution and morphology is so remarkable as to merit detailed description. In the first specimen removed from the ascending colon, the giant cells while easily

found are not especially numerous, and are distributed equally throughout all coats of the intestine. They are large, have irregular dentated outlines and contain numerous nuclei irregularly distributed. They have none of the characteristics of either the giant cells of the Langhans type or the Reed-Sternberg type. A careful search reveals no evidence of foreign body in or contiguous to these cells. In the specimen of the small intestine removed from this patient, the giant cells are extremely numerous, three or four being present in almost every field. While morphologically they resemble the giant cells found in the colonic specimen, in these a foreign body is found within the majority of these cells. These foreign bodies have a varying morphology, usually they are round, oval or biscuit in shape, with a granular or highly refractile content and a dense lamellated capsule. What these foreign bodies are we have not been able to determine. They do not even afford the possibility of a guess.

In none of our specimens is there the slightest evidence of necrosis or caseation.

In Cases I and II, sections were stained for tubercle bacilli and the *Spirocheta pallida* but were not found. Bacterial stains on Cases III and IV were not made.

Sections of the mesenteric lymphatic glands reveal nothing noteworthy.

Discussion. It is a remarkable fact that non-specific inflammatory tumors of the intestine were, with few exceptions, not described until 1908. Practically the entire literature upon the subject dates from the publication of Braun¹ in that year, and it is his report that has stimulated subsequent studies. It is true that in 1898, Graeser, in a classical paper, called attention to inflammatory processes in the sigmoid flexure arising from acquired diverticula, but such lesions, although morphologically similar to those in which we are interested, do not enter into our discussion. The reason of this curious absence of comment is the fact, as we shall discuss more fully in a subsequent part of this paper, that these cases were regarded as instances of "hyperplastic tuberculosis of the intestine."

Braun's case was that of a woman, aged forty-three years, who presented a tumor on the left side of the abdomen of eight weeks' duration. The bowels were irregular, often tinged with blood. Diagnosis, carcinoma. At operation a mass in the sigmoid flexure was found which involved mostly the mesenteric aspect. The mucosa covering the growth was normal. Microscopically the tumor consisted of a poorly cellular connective tissue infiltration of the meso-sigmoid which extended partly into the muscularis and the submucosa. In one portion there was a broad streak of round celled infiltration which penetrated to the mucosa.

The number of case reports since Braun's publication has been

large and year by year shows a progressive increase, so that it is safe to say the malady is not at all a rare one.

We do not propose to submit a complete digest of all the literature pertaining to the subject. Those interested may refer to the fairly complete and most recent studies of Tietze² and Körte.³ We shall merely content ourselves with giving a summary of the pathology, some of clinical aspects and the etiology.

PATHOLOGY. Each of our cases exemplifies in one way or another the characteristics common to this lesion. There is a tumor of greater or lesser size which may involve any portion of the colon. Even in the sigmoid many such lesions are described without in anyway being associated with a diverticulitis. The inflammatory process usually involves all the coats of the intestine. Sometimes the proliferation is most prominent in the inner coats forming smaller or larger tumors which narrow the lumen of the gut. Less frequently the proliferation seems to begin in the mesenteric attachment forming tumors sometimes even as large as a child's head, which involve the walls of the gut by continuity and cause stricture of the lumen. In the former, there is ulceration of the mucosa, which, as a rule, is superficial and not extensive; in the latter the mucosa appears perfectly normal or slightly thickened. Adhesions to surrounding structures and to the abdominal wall are common. In a few instances, the induration has extended to the ileo-cecal valve causing narrowing of this structure. Abscess formation is rare, and when present is slight as in one of our cases.

MICROSCOPICALLY. These tumors reveal typical granulomatous changes in various stages of senescence and the descriptions we have submitted in reporting our cases (excepting Case I which is almost unique) cover the ground quite fully. There is never the slightest evidence of tuberculosis, syphilis, lymphogranulomatosis or new growth.

The remarkable resemblance of some of the cases which we report to hyperplastic tuberculosis of the intestine led us to a study of the literature of this malady in order to check up our findings. We have arrived at the conclusion that undoubtedly many if not a majority of so-called "hyperplastic tuberculosis of the colon" are really simple granulomata. Indeed the majority of authors of comprehensive papers on "hyperplastic tuberculosis of the intestine" describe lesions that are identical in every way to those which we have reported. For instance Lartigau⁴ says, "More often the tubercles are mere aggregations of lymphoid cells in which one or more giant cells are seen. Epithelioid cells are usually absent. Many show little tendency to necrotic change; a distinct tendency to fibrous transformation is apparent. *The typical histological features of tubercle bacilli are often absent*; in lieu thereof there may exist a diffuse embryonal cell differentiation, at times capable of simulating sarcoma." Ignard⁵ says, "In many

cases of hyperplastic tuberculosis of the intestine, no tubercles, giant cells or bacilli are found. The lesion is constituted of a mixture of variable proportions of tuberculous and inflammatory elements. *In certain cases, the last only exist.* Nevertheless, these inflammatory tumors should be classified among the tuberculous." Itie⁶ says, "The tuberculous elements are relatively rare. More often you find simple follicles with two or three giant cells. The zone of epithelioid cells is wanting, and only a crown of round cells surrounding a giant cell is found." Pilliet and Hartman⁷ say that "Hyperplastic intestinal tuberculosis differs from the common tubercle. The tuberculous follicles are relatively rare; the embryonic infiltration on the other hand is more marked." Weiting⁸ after calling attention to the fact, "That tuberculosis may cause an immense amount of connective tissue infiltration without any tendency to break down," remarks in a late portion of his paper, "that a diagnosis of tuberculosis must be excluded unless tubercles with giant cells are present." Shiota⁹ who describes 24 cases of so-called hyperplastic tuberculosis remarks, "That it is common not to be able to differentiate the lesion from an inflammatory hyperplasia." Ipsen¹⁰ says, "That tuberculosis may be present even though the characteristic histological reaction is absent, and that the diagnosis can only be confirmed by animal inoculation." Incidentally, as regards intestinal tuberculosis, we have been unable to find in the literature that this procedure has been performed. He regards "a late invasion by the organism as a possible explanation for the absence of the characteristic histological characters." Doubt seems to have crept into the mind of but one observer, Richter.¹¹ He believes that hyperplastic tuberculosis is really a non-specific inflammation of the cecum and that the tuberculosis is only an accidental infection and complication, the result of swallowing tubercle bacilli either from a pulmonary focus or in milk.

It does not require much reading of studies of intestinal tuberculosis to discover that observers have copied each other's discussions closely. For instance, nearly all try to account for the non-tuberculous characteristics of their lesions by likening them to lupus. It remained for Richter to disclose the fallacy of this assumption. Furthermore, all comment on the sparseness, or what is more significant, the absence of tubercle bacilli in such tissues, although only very few mention any attempts at finding them in the lesions they report. At all events, the scarcity of bacilli is supposed to account for the absence of the typical histological characters of tuberculosis in these lesions, but on what grounds we do not know. Tubercle bacilli are scarce in many frankly tuberculous lesions, but nevertheless, the lesions are unmistakable. The absence of bacilli in the lesions they describe is certainly significant, but this seems to have escaped notice.

We believe, therefore, with more rigid methods of histological study, the number of true hyperplastic tuberculoses of the intestine will diminish appreciably and that in the future fewer will be reported than heretofore.

The criticism we have submitted also accounts in a large measure for the comparative absence of reports of non-specific granulomata of the intestine up to the year of Braun's publication.

ETIOLOGY AND PATHOGENESIS. In the vast majority of the reported cases the etiology was unknown. A curious feature in all 4 cases which we report is the history of a previous appendicitis or appendectomy. In 2 cases (I and III) a definite acute suppurative appendicitis preceded the onset of signs six months and two years respectively. In Case II an appendectomy in the course of herniotomy was performed three years previously. (Whether the appendix was diseased or not can no longer be determined.) In Case IV the history suggested an acute appendicitis three weeks previous to the onset and pathological examination of the appendix revealed a completely obliterated organ.

The relationship of inflammatory lesions of the colon to appendicitis is repeatedly broached in reported studies. (De Ruyter,¹² Gangitano,¹³ Låwen,¹⁴ Gato,¹⁵ Teitze,² Körte.³) In most of these reports however, the inflammatory process is continuous with that of the appendix and involves only the contiguous portion of the cecum. In other instances mere coproliths are present or old obliterations at the tip. Despite the frequent associations of inflammatory lesions in the colon and appendicitis, we are forced to the conclusion, taking into consideration all possible genetic factors, that this relationship is entirely coincidental. We cannot conceive how a chronic granuloma in the colon can arise at a distance from an inflamed appendix removed six months or two years previously or an appendectomy performed three years before the onset of signs. Even if such a late infection were possible, it could only arise by way of the lymphatics, and while it is true according to Bartels¹⁶ that the lymphatics of the appendix and cecum anastomose, the current is in the reversed direction. To assume that an infection occurs in the retrograde direction would be stretching possibilities unduly. Another possibility is that the presence of a dormant infection in the gut contributed to an infection of the appendix. There is little question, judging from the morphological characters, that the granuloma was present in the gut long before clinical manifestations became apparent and it is conceivable that such a mass, probably already ulcerated, would render an infection of the appendix more liable. In this connection it is interesting to note that a primary typhlitis of the cecum, a lesion resembling those which we describe very closely has been reported occasionally, in many instances such a lesion being regarded as the source of a subsequent appendicitis. For many years the occur-

rence of a primary typhlitis was doubted but it unquestionably occurs. Haim¹⁷ reports many such.

There are a number of case reports of granuloma of the colon in which foreign bodies were the direct cause. Jaffe¹⁸ found a tumor the size of a fist involving the colon in the center of which a small piece of bone was found. Schreiber¹⁹ reports a large ulcerating granuloma of the ileo-cecal region in which many cherry and plum pits were present. Marion²⁰ reports a piece of bone in a large granuloma of the ascending colon adherent to and involving the rectus muscle. Tietze² reports a granuloma in the cecum following an operation for acute appendicitis. In the center of the granuloma the silk thread employed in ligating the appendix was found. Wölfler and Lieblein²¹ in their comprehensive monograph on "foreign bodies in the intestine" remark on the frequency of lodgement of such bodies in the cecum where they give rise to large inflammatory thickening with adhesions and occasionally to perforation with chronic abscess formation.

The only specimen in our series in which a foreign body was present is Case I in which microscopical foreign bodies of unknown structure were found enclosed within giant cells. What the nature of these structures are is unknown to us. These foreign bodies we believe penetrated into the wall of the gut through previous ulceration consequent to colitis. No foreign bodies were found in the other specimens, either on section or by roentgen-ray.

A colitis or dysentery has been reported as preceding the onset of these granulomata by numerous writers, (Monsarrat²², Rosenheim,²³ Strauss,²⁴ Birt and Fisher,²⁵ Koch,²⁶ Gato¹⁵ and Tietze²). In our first case a colitis was probably the origin of the granuloma, if a long standing diarrhea with blood and mucus in the stool is at all diagnostic of a colitis. Tietze reports a case of inflammatory tumor of the sigmoid flexure following irrigation of the lower bowel with a strong silver nitrate solution.

The derivation of granulomata from diverticulitis of the sigmoid is well known. This malady, however does not enter into our discussion.

In the vast majority of instances the cause of the granuloma is unknown. We must presume that there is some infectious agent of low grade violence which enters through the mucosa. Distribution of the infection by lymphatics is in most instances highly probable. The lesions remind one strongly of the granulomata described by Braun²⁷ and others which occur in the omentum following ligation and resection of this structure in herniotomies and which are due to infections from silk or catgut. Rarely, these granulomata arise from infections in the stomach, Fallopian tubes or ovaries. They also resemble the inflammatory tumors of the abdominal wall described by Schloffer,²⁸ arising after operations

for hernia in which silk stitches are occasionally found imbedded within the tumor.

CLINICAL CONSIDERATIONS. A survey of our report readily leads to the deduction that the lesion we report offers no characteristic clinical concept: the etiology, symptoms and signs are too protean and indefinable. Evidence of a stenosis of the gut and the presence of a mass in the abdomen are by all odds the most constant phenomena. The most prevalent diagnoses have been malignant growth, hyperplastic tuberculosis and appendicitis and most observers agree that a correct preoperative diagnosis is impossible. The most interesting and diagnostic characteristic in connection with these granulomata of the intestine is their disappearance after a simple sidetracking operation. Moynihan²⁹ and Robson³⁰ report such instances. Obviously the presence of a tumor of this variety has a profound bearing on prognosis.

Conclusions. 1. Four cases of non-specific granulomata of the intestine are described. All involved the colon, 1 involved both colon and small intestine.

2. The histological characteristics are those of a simple granuloma. No evidences of tuberculosis, syphilis or lymphogranulomatosis are present.

3. The granulomata may involve any portion of the colon. The infiltration of the wall may be more prominent on the mucosal or the mesenteric aspect. In both instances the lumen is narrowed. Ulcerations, which are usually superficial, may be present; exceptionally, abscess formation.

4. The cause most often is unknown. In a few cases foreign bodies and a colitis have been reported. Despite the association of the lesion with a previous appendiceal involvement we do not believe that appendicitis has any direct causal relationship to the malady.

5. Clinically, these cases present signs of constriction of the intestinal lumen and a mass in some portion of the colon. Thus far, they are not diagnosticable before operation and have usually been mistaken for carcinoma and tuberculosis of the intestine. Not infrequently these tumors disappear after simple sidetracking of the intestine. The prognosis is excellent.*

* We wish to express our profound thanks to Drs. Seward Erdman, W. C. Clarke and P. Stout for the privilege of reporting their cases.

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A POSSIBLE RELATIONSHIP BETWEEN THE CURRENT OF INJURY AND THE WHITE-BLOOD CELL IN INFLAMMATION.

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THE study of inflammation has resulted in the formulation of many hypotheses of the causes and the results of the processes present. For the purposes of the experiments upon which this paper is based, inflammation is regarded as a process incidental to some injuries in living tissues; more particularly, the congregating of cells in the zone of injury is considered the essential feature. There is inflammation, and there must be present in the tissue where the process occurs some system of factors which brings certain tissue units to the point of injury, and the cells influenced must be able "mechanically" to reach the point of excitation. The questions of how and why the white-blood cell arrives at the point of injury have been widely discussed. Neglecting the teleological attitude, and without going into a discussion of chemotaxis, surface tension, and so on^{1, 2} which have been offered as possible explanations and which certainly may play a part, this paper, first, will endeavor to offer an hypothesis which will eventually attempt to correlate qualitatively and quantitatively the chemical and mechanical make-up of tissues with the migration of the white-blood cell to some points of injury; secondly, will present some experimental evidence in favor of this hypothesis; and thirdly, in discussion will elaborate upon the first two.

I. The Basis of the Hypothesis. Although all injuries to cells or tissues are not followed by the microscopical picture of inflammation, inflammation is always an expression of injury. When living tissues are injured, whether the fashion be crushing, burning, cutting, or chemical, there ensue the visual and chemical changes which follow such interruptions of normal tissue metabolism. If a living leaf be cut, and non-polarizable electrodes be applied to both injured and

uninjured surfaces,³ there is experienced an electro-motive force between the cut and uncut surfaces. Similarly, if a carefully dissected frog's muscle be cross-sectioned, and non-polarizable electrodes be applied in the same fashion, the injured surface becomes electro-negative and the galvanometer's deflection slowly increases to a maximum, after which it suffers a parallel diminution until it eventually disappears. This current of injury varies with the point of application of the electrode upon the uninjured surface, and is not one due to membrane potential phenomena alone, but because of the fact that between the injured and normal tissue there passes when injury is produced, a more or less constant current which varies in intensity as the many factors of tissue and tissue injury do. Uninjured muscles in the resting state are iso-electric; no difference of potential is manifested at their surfaces.^{4, 5}

Hermann, who made the observations noted above, formulated the law which is applicable to all cases, that, "In every injured muscle fiber the surface of demarcation between the living and dead (or rather dying) portion of the fiber is the seat of an electro-motive force toward the living part." Another related fact brought out by this author is that a general rise of temperature increases the strength of this demarcation current up to a certain limit beyond which it decreases again, until it disappears with the onset of heat rigor.

In the same fashion the currents that can be led off to a galvanometer from an artificial cross-section and from any given point of the uninjured longitudinal surface of a nerve increases, and then decreases one-half in two to four hours. But the difference of potential may increase again, and the current regain its original force if a new section is made near the first.⁶ This fact is important because it seems that the strength of the current is not only influenced by temperature at the site of injury, but also the degree of the lesion. The strength of these demarcation electro-motive forces varied from .02 to .03 of a volt in the frog's sciatic nerve, and was equal to .008 of a volt in that of a horse (Biederman). It has been known to exceed .08 of a volt in a frog's gastrocnemius (Du Bois Raymond).⁷

The significance of these currents of injury in relation to the theory of leukocyte mobility and to inflammation soon to be discussed, is more readily appreciated if the injured tissue and the adjacent normal or nearly normal cells be compared to an electric battery.⁸ From the facts enumerated above it is apparent that injury to living tissues precipitates primarily an increase in chemical activity, one of the manifestations of which is the electrical phenomena observed. This increase in chemical activity may be compared to that which takes place in a battery having zinc and copper plates as electrodes which are immersed in solutions of their respective salts and separated by a porous partition.

1. The pole⁹ on the left becomes negatively charged on account of the departure of positively charged ions from its surface, for this metal, zinc, goes into solution more rapidly than does copper. A

current therefore, according to conventional usage, flows from positive to negative through the wire and in the form of migrating ions from positive to negative through the liquid.

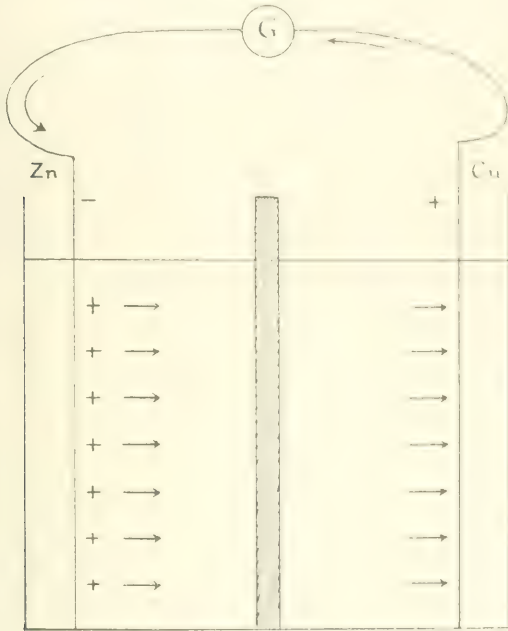


FIG. 1.—Schema to show direction of current in battery.

2. The difference in potential (E. M. F.) is not affected by changes in the size or shape of the poles or the amounts of the solution, provided the materials are not changed. It is very noticeably altered, however, by changes in the concentrations or the type of solution.

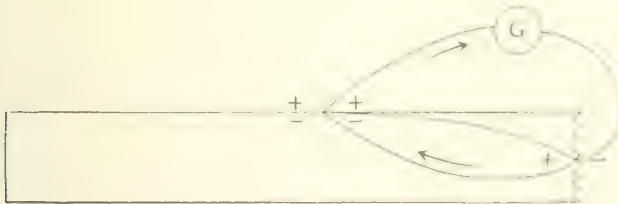


FIG. 2.—Schema to show path of demagnetization current.

To resume the comparison of an injured tissue to a battery, the uninjured surface may be considered the positive pole and the injured the negative, the current flowing externally from positive to negative. Internally, the injured tissue may be compared to the immersed zinc plate—the normal to the immersed copper plate and hence the injured area will be electro-positive—the uninjured electro-

negative, and the current flow from the injured to the uninjured cells.

If there be between the normal and injured tissues a current flowing which would vary with the type of tissue, degree of injury, temperature of the part, and if in this electrical field there be free cells and injured bloodvessels, the hypothesis, that one of the forces guiding the white-blood cell to the point of injury (and perhaps even playing a dominant role) is the electrical current flowing between the injured and uninjured tissues, is hardly without reason. The concept that the white-blood cell may go toward one pole or another is not new. But the pole to which they migrate has not been settled. For the past thirty years numerous observers have disagreed because the experimental conditions under which they worked were different. Platinum poles instead of non-polarizable electrodes were used; sugar or other solutions held the blood cells in suspension.^{10 11 12} The hydrogen-ion concentration of the medium was neglected. The knowledge of the influence of pH on cataphoresis and proteins in general is a recent acquisition.

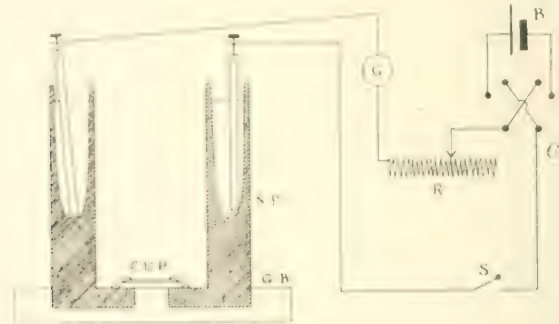


FIG. 3.—Diagram of apparatus; B, battery; C, commutator; C.D.P., coverslip and serum surrounded by paraffin; G, galvanometer; G.B., glass block; N.P., non-polarizable electrodes; R, rheostat; S, switch.

The technic to be described obviates as far as possible the errors mentioned above, and although the experiments to be presented were done *in vitro*, it is fair to draw some parallelism between them and the changes in the living tissue. Unglazed porcelain non-polarizable boot electrodes were set in a glass block 5 mm. apart and ground down so that the level of the electrodes and glass were the same. The apparatus was kept in physiologically normal saline whose pH was about 7.5, approaching that of serum. While on a warm stage at about 100° F., the effect of the passage of a current from a dry cell through human serum containing the cells of the uppermost layer of centrifuged defibrinated blood was observed. The coverslip over the drops was surrounded by paraffin, and thus preventing evaporation, preparations could be studied for hours. A shunted galvanometer recorded the passage of the current and a pole changer was in the circuit.

II. Experimental Evidence. The following observations have been made with the technic which was described most briefly in the preceding paragraph.

1. Small lymphocytes, when the estimated difference of potential between the two electrodes is .4 of a volt and the current through the circuit $\frac{1}{25}$ of a milliampère, migrate toward the positive pole with a speed approximately of 15 microns per minute.*

They move faster than red blood cells in the same preparation, pushing them aside and traveling almost in a straight line. When the current is reversed they almost instantaneously change the direction in which they are traveling. All the lymphocytes in the field do not migrate. Those which seem physically able to do so invariably travel toward the positive pole, or, comparing it to the injured tissue, to the electrical equivalent of the point of injury. Although tiny processes seem to be thrown out, there could hardly be said to be much, if any ameboid motion, and the migration could in all probability be considered a result of cataphoretic phenomena.

The speed of migration was not dependent upon the "age" of the lymphocyte. Approximately the same velocity was shown by lym-

* There are numerous technical difficulties attached to the use of the apparatus described in these experiments. A recent article by Winslow *et al* (Jour. Gen. Physiol., 1923, 6, 177) takes up some of these, and gives rather complete references to the theoretical considerations. The presence of glass particularly influences the speed of migration of particles suspended in a watery medium. Water is electro-positive to glass. "That is, the water which moves toward the cathode at the glass surfaces returns toward the anode in the mid-regions of the fluid in the cell. Obviously then, the electrophoretic movement of the particles will be impeded at certain levels in the cell and accelerated at others by the independent movement of the water. In addition, of course, there is the electrical endosmose, due to difference of potential between the particles and the water. The true mobility of the particles is the average mobility of all levels in the cell."

In the experiments of the author there were many mechanical drawbacks, especially the tendency of the white-blood cells to settle upon the glass block, thus preventing an attempt to determine "the true mobility of the particles"—the lymphocytes. The cells whose average speed was 15 microns per minute were those which moved. There were also present in the field red blood cells and leukocytes, although an attempt was made to get only white blood cells from the uppermost layer of the defibrinated human blood with delicate capillary pipettes. Many of the lymphocytes, particularly those resting on the glass, exhibited no movement in either direction. Those which did move always moved toward the anode. Hence the figures given in this report for lymphocytic speed under the experimental conditions is not the "true mobility" of the lymphocyte under those conditions, but is an expression of the direction of migration of the lymphocyte, aided in speed, presumably, by the anodal flow of water in the mid-regions of the cell.

In the Helmholtz-Lamb equation,

$$P.D. = \frac{4\pi n v}{K X}$$

in which:

- n = viscosity of the solution.
- v = velocity of the particle in centimeters per second.
- K = dielectric constant of the solution.
- X = potential gradient.

All electrical units expressed electrostatically, *cannot* be used with the figures reported for the speed of the lymphocytes to determine the potential difference (P.D.) between the lymphocytes and the serum in which they were suspended, because of a lack of knowledge of their "true mobility."

phocytes which were obtained from freshly drawn blood and by those which had been kept on ice for thirty hours or less.

2. Polymorphonuclear leukocytes, under the same conditions, exhibited nothing which could be called a constant direction of migration. The experiments were entirely negative as far as this type of blood cell was concerned. Since unicellular organisms, including ameboid forms, in general under the proper electrical and mechanical conditions move toward one pole or the other,^{13, 14, 15, 16, 17, 18} it should be expected that the movements of the polymorphonuclear leukocyte would also be influenced by the galvanic current. At present a direct analogy cannot be made with the ameba because the observations were not made under known conditions of hydrogen-ion concentration. The effects of glass and of the presence of light, the absence of chemical substances accompanying tissue injury, the need of a stronger current and the mechanical conditions may influence ameboid movement in the leukocyte. In this connection, the effect of glass on the cataphoresis of bacteria,¹⁹ the influence of light on the ameba,²⁰ the change in direction of migration of paramecium brought about by chemical substances²¹ are both interesting and important. For in all probability these factors and the mechanical limitations (*e. g.*, polymorphonuclear leukocytes upon meeting a roughened crack in glass almost invariably ceased to move) play an important rôle in the failure of the experiments. Even tissue cultures grow in line with a constant current and perpendicular to a conductor.²² The applicability of this work to the repair of tissue injury, to the growth of bloodvessels into granulation tissue and its own formation, is most suggestive when considering the electrical phenomena incidental to injury.

III. The Elaboration of the Theory. Several questions have been asked. Will leukocytes under the experimental conditions react to a stronger current? Are the mechanical conditions present conducive to migration? Does light inhibit their response to the electric current? That is, under the experimental conditions may there not have been many other factors which influence the direction of the leukocytic migration over the pathway described and that observed be a resultant of these forces?

In answer, the following elaboration of the theory is presented purely as speculation based upon the physiology and pathology of inflammation as well as what has been described. In the presence of an acute infection* there are manifested the signs of an increase in chemical activity, and were the demarcation current to be measured, it should be greater than that produced by a low grade inflammatory process. In terms of the current of injury therefore, chemical phenomena are set up in the chronic process which do not produce as intense a current as in the acute process. With a weak constant current are attracted the slow moving lymphocytes; with the stronger current, the greater tissue injury, and perhaps with the

* Or only soon to injury.

production of leukocyte stimulating substances there rush, directed by the demarcation current plus the other factors, the leukocytes and some lymphocytes. As the chemical activity abates and the leukocytes disintegrate, there remains a small but constant current sufficient to maintain a steady lymphocytic migration. And with the further waning of the electrical phenomena, there are fewer and fewer white-blood cells wandering to the site, until with the cessation of the current, the migration ends.

In further support of this point of view is the reaction of the tissues themselves. If they be listed according to the ease with which an inflammatory process be set up within them, it will be found to be a function of the chemical response to injury and hence a function of the demarcation current. That is, connective tissue responds more readily than cartilage to injury, tendon less than connective tissue. The character of chemical make-up of the tissue produces a great number of physical and chemical changes in response to injury, the resultant of which is an index of what the demarcation current would be. Experiments by W. C. Clarke and W. C. Woolsey lead one to suspect that hyaline cartilage does not respond to injury by the usual process of repair. A summary of one of the experiments follows: In dog No. 116/85, January 28, 1914, forty-nine days after incision of the cartilage of the humeral head, the surface appeared grossly as if no attempt at repair had taken place. Microscopical examination bore out the gross findings. A "V"-shaped defect into the cartilage, but not through to the underlying bone, revealed no morphological suggestions of repair or change in the surrounding cartilage cells.

If the injury had been one that involved a greater chemical response would the microscopical reaction have been different?

The mechanical limitations to reaction within a tissue like tendon or cartilage also plays its part. Even if the current were strong enough in cartilage, which apparently does not set up a true "chondritis," could the white-blood cell overcome the resistance offered by the poor transits for cellular migration?

The following further experiments would partially determine the appropriateness of the outlined hypothesis.

1. The study of the response of leukocytes and lymphocytes to different currents and electro-motive forces under varying conditions (*e. g.* in the presence of extract of tissue, etc.).

2. The measurement of the demarcation currents of different tissues under standard conditions and their comparison with those used experimentally.

3. The demonstration of the effect of the electric current *in vivo*.

4. The reaction of clinical material treated by the principles of the inflammatory process as cited above.

Summary. 1. A theory is offered that one of the forces guiding the white blood cell to a point of injury followed by an inflammatory process may be the current of injury (demarcation current).

2. With non-polarizable electrodes under stated conditions, small lymphocytes migrate toward the anode which may apparently be compared to an injured tissue focus where inflammation has set up.

3. Polymorphonuclear leukocytes under the same conditions do not consistently go toward one pole or the other. The probable cause of their failure is discussed.

4. The speed of 15 microns per minute manifested by small lymphocytes was the same whether freshly drawn blood cells were studied, or those taken from defibrinated blood kept on ice up to thirty hours.

5. Little if any ameboid motion was observed during lymphocytic migration.

6. Those tissues which respond most easily with the picture of inflammation to injury, should have the greatest currents of injury, thus correlating the view expressed with the pathological processes.

7. The mechanical and chemical make-up of tissues is stressed as a deciding factor in ease of production of the picture of inflammation.*

* The author desires to express his sincere thanks to William C. Clarke, and Arthur R. Sharp, of the Department of Surgery, and to Professor Horatio B. Williams, of the Department of Physiology, for the aid and criticisms received during the experimental work and the writing of this paper.

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4. Hermann, D. L.: *Handbuch der Physiol.*, 1879, **1**, 192.
5. Biederman W.: *Elektrophysiologie*, Jena, 1895, p. 274.
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11. Dineur: *Bull. Soc. belge de micro.*, 1891-92, **28**, 113, quoted by Putter, E., *Loc. cit.*, p. 539.
12. Lillie, R. S.: *Am. Jour. Physiol.*, 1903, **8**, 273.
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17. Kosaka and Siki: Quoted by Putter, E., *Loc. cit.*, p. 539.
18. Putter, E.: *Loc. cit.*
19. Putter, E.: *Loc. cit.*
20. Schaeffer, A. A.: *Reaction of Amoeba to Light*, *Science*, 1914, **39**, 474.
21. Abrahamson, A. B.: *The Effect of Galvanotaxis in Paramoecia by Chemical Substances*, University of California Publications in Physiology, 1906, **3**, 21.
22. Ingvar, S.: *Reactions of Cells to the Galvanic Current in Tissue Cultures*, *Proc. Soc. Exp. Biol. and Med.*, 1919-20, **17**, 198.

THE CHEMICAL PATHOLOGY OF PYLORIC OCCLUSION IN RELATION TO TETANY

A STUDY OF THE CHLORIDE, CARBON DIOXIDE AND URIC ACID CONCENTRATIONS IN THE BLOOD *

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Gastric tetany, that form of nerve hyperirritability associated with vomiting, dilatation of the stomach and pyloric occlusion, has interested and puzzled physicians for years. The condition is included in the realm of surgery, since it is usually the result of a gross lesion near the pylorus, and, consequently, its cure depends on operative measures. The clinical literature on the subject has established no definite etiology and the various theories proposed to explain the relationship between the disturbance of gastric physiology and tetany have been unconvincing.

In this paper are recorded the clinical histories and blood analyses of seven cases of obstruction at or near the pylorus, with a summary of the results of some experimental work on dogs. The facts to be presented support the theory that directs attention to the loss of hydrochloric acid from the stomach as the cause of critical changes in the composition and physiochemical properties of the blood. Thus is altered profoundly the "milieu interieure"—the disturbance of whose regulated balance produces such profound changes in the dynamics of protoplasm. In this case, the tissue most conspicuously affected is that of the peripheral nervous system, which shows a progressive increase in irritability. The outward manifestation of this hyperirritability is the clinical condition known as tetany. As other cells of the body are similarly exposed to the disequilibrated blood, there are probably further significant derangements, the nature of which is still a matter of conjecture. These may overshadow in critical importance the nervous condition, and might, if known, be more justly held accountable for the frequently fatal outcome.

HISTORY

Kussmaul,¹ who seems to have been one of the first to differentiate and describe gastric tetany, once believed it to be the result of tissue desiccation. Bouveret and Devie,² and later Mayo-Robson,³ suggested that the absorption of stagnant stomach contents produced the carpopedal spasms. Germain-Sée⁴ favored the idea that the somatic nervous

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1. Kussmaul, A.: *Deutsch. Arch. f. klin. Med.* **6**, 1869.

2. Bouveret and Devie: *Rev. de méd.* **12**:48, 1892.

3. Mayo-Robson, A. W.: *Lancet* **2**:1392, 1898.

4. Germain Sée, quoted by Mayo-Robson and Mornihan (Footnote 5).

tetanus was a reflex arising from a dilated and hyperirritable stomach.

In many cases there is undoubtedly considerable dehydration, as evidenced by thirst, oliguria, loss of tissue turgor, dry tongue and increased proportion of cellular elements in the blood; but that desiccation is not the cause of the tetany is shown by the fact that experimental tetany develops after pyloric occlusion, in the absence of any apparent thirst and without a change in the normal ratio of cells to plasma. The fluid balance is easily maintained by introducing water into the duodenum, i. e., below the obstruction.

As regards autointoxication, one receives a contrary impression in reviewing clinical case histories, namely, that the emptying of the stomach either through persistent vomiting or by frequent gastric lavage is a significant factor in the production of tetany. MacCallum found that tetany could be rapidly initiated after experimental pyloric occlusion in dogs by frequent washings, and in our experiments the most marked example of tetany developed in a dog whose stomach was thoroughly lavaged two or three times a day. In the face of this evidence, it does not seem that the absorption of stagnating stomach contents could be the cause of tetany, since the latter condition developed when there was no stagnation. In fact, it would seem that the expulsion of stomach contents rather than their introception precipitated the seizures. Moreover, there is normally little absorption from the stomach. In many of the cases in human beings little food was taken, and in all cases of dogs, no food was taken; so that the absorption of products from the fermentation and putrefaction of exogenous substances can be eliminated as a factor. Mayo-Robson's autointoxication theory is possible only on the assumption of vascular absorption of poisonous products from a stomach wall showing no signs of a gross or microscopic pathologic condition, the inner lining of which is being regularly irrigated. The reflex theory has no direct experimental evidence to substantiate it and seems to have few advocates among modern surgeons.

These views were presented at a time when experimental methods of a certain type were crude and speculation was rife. It seems hardly necessary at present to subject them to more detailed and analytic scrutiny.⁵

5. I have been unable to find any recent or comprehensive accounts of gastric tetany. For a short general description of the symptoms, course and treatment, the reader is referred to Mayo-Robson and Moynihan (*Surgical Treatment of Diseases of the Stomach*, Ed. 2, New York, 1904, p. 408); for a bibliography and a discussion of the experimental work and the theories of etiology to Trevelyan, E. F.: *Lancet* **2**:79, 1898; Halliburton, W. D., and McKendrick, J. S.: *Brit. M. J.* **1**:1607, 1901, and McKendrick, J. S.: *Scot. M. & S. J.* **21**:253, 1907; and for clinical reports to Cunningham, J. H. *Ann. Surg.* **39**:527, 1904; Brown, J. Y., and Engelbach, W.: *Am. J. Obst.* **58**:970, 1908, and Rodman, W. L.: *Gastric Tetany*, *J. A. M. A.* **62**:590 (Feb. 21) 1914.

EXPERIMENTAL WORK AND THE ETIOLOGIC CONSIDERATIONS

The original impetus to the study of tetany from the standpoint of the acid-base equilibrium was given by Wilson and his co-workers,⁶ who investigated the form which follows parathyroidectomy. MacCallum⁷ first studied chemical changes after pyloric occlusion, and discovered that there was a marked rise in the carbon dioxid capacity of the blood after this operation. This work, together with the investigations of McCann⁸ and some performed in the surgical research laboratories of this college,⁹ constitutes the only experimental work published on the subject within recent years. There were no important disagreements in data. The results indicated that, after pyloric occlusion in dogs, there was a rapid and marked increase in the carbon dioxid capacity, and a significant fall in the concentration of chlorids in the plasma. The calcium and the sodium content of the blood was not thoroughly investigated, but the few tests made seemed to show a slight rise in calcium and a fall in sodium. Some support for the high calcium values has been presented in a recent clinical report by Grant,¹⁰ and for the subnormal sodium figures by the analyses of Tisdall.¹¹ A definite rise in sulphur and phosphorus was found. In our series of experiments, there was a moderate increase in p_H as measured electrometrically in three out of four dogs, a change which was considered too small to account for the nervous hyperirritability.

With the above mentioned findings at hand, we were inclined to believe that the increased irritability was the result of a disturbance in the relative concentration of anions, i. e., decrease of chlorid, and increase in carbonate, phosphate and sulphate ions, rather than a change in hydrogen concentration. The effect of anions of different valences on the colloidal state has been studied by biochemists, and was found significant in numerous instances. MacCallum called attention to the low chlorid concentration as a possible etiologic factor when he found that sodium chlorid was more effective than hydrogen chlorid in preventing canine gastric tetany. Collip,¹² and later Tisdall,¹¹ emphasized the effect of an increased concentration of HCO_3^- ions, and Green-

6. Wilson, D. W.; Stearns, T., and Janney, J. H.: *J. Biol. Chem.* **21**:469, 1915. Wilson, D. W.; Stearns, T., and Thurlow, M. deG.: *J. Biol. Chem.* **23**:89, 1915.

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8. McCann, W. S.: *J. Biol. Chem.* **35**:553 (Sept.) 1918.

9. Hastings, A. B.; Murray, C. D., and Murray, H. A., Jr.: *Biol. Chem.* **46**:223 (March) 1921.

10. Grant, S. B.: Tetany, *Arch. Int. Med.* **30**:355 (Sept.) 1922.

11. Tisdall, F. F.: *J. Biol. Chem.* **54**:35 (Sept.) 1922.

12. Collip, J. B.: *Am. J. Physiol.* **52**:483 (July) 1920.

wild,¹³ in a summary of existing hypotheses, stressed the anion equilibrium to which he assigned a control over the permeability of the nerve sheath to the cations.

More definite and applicable data is available dealing with cations, particularly the effect of changes in the sodium:calcium ratio on the irritability of nerves.¹⁴ The increase of the ratio, i. e., the relative increase in the concentration of the sodium was found to increase the irritability of nerve tissue; whereas, the addition of calcium would depress it. The importance of this ratio, or, more generally, the monovalent cation:divalent cation ratio, was affirmed by Fühner,¹⁵ and later reemphasized.¹⁶ This view seems to be supported by the studies of tetany following parathyroidectomy,¹⁷ and of idiopathic infantile tetany,¹⁸ and by experimental infusions of sodium salts in dogs,¹⁹ the injection of calcium precipitants²⁰ and the results of too vigorous saline or bicarbonate therapy in human beings,²¹ intravenously²² or by rectum.²³

But it is evident that, by the injection of sodium bicarbonate and sodium phosphate, salts that have been used most frequently in experiments, not only is the sodium increased and calcium decreased, more than can be accounted for in the blood by mere dilution, but also there are added alkaline factors which may be sufficient to increase the p_{H}

13. Greenwald, I.: *Proc. Soc. Exper. Biol. & Med.* **18**:228, 1921.

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18. Howland, J., and Marriott, W. McK.: *Quart. J. Med.* **11**:239 (July) 1918. Jacobowitz, S.: *Jahrb. f. Kinderh.* **92**:256, 1920. Brown, Alan; MacLachlan, I. F., and Simpson, R.: *Effect of Intravenous Injections of Calcium in Tetany and Influence of Cod Liver Oil and Phosphorus in Retention of Calcium in Blood*, *Am. J. Dis. Child.* **19**:413 (June) 1920.

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21. Grant, S. B.: Footnote 10. Tileston, W., quoted by Palmer, W. W., and Van Slyke, D. D.: *J. Biol. Chem.* **32**:499 (Dec.) 1917.

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23. Healy, W. P.: *Am. J. Obst. & Gynec.* **2**:164 (Aug.) 1921. Campbell, O. H.: *A Peculiar Case of Common Salt Poisoning*, *J. A. M. A.* **59**:1290 (Oct. 5) 1912.

of the blood and thus affect nerve irritability. There is evidence to show that nervous irritability is a function of the hydron concentration and that increasing the p_H may cause tetany. The most substantial proof is afforded by the valuable studies of Grant and Goldman,²⁴ who showed that tetany could be produced experimentally in man by forced breathing. The disturbance in the acid-base equilibrium which was probably responsible for the neuromuscular irritability was evidently caused by the rapid expirations by which carbon dioxide was thrown off. This diminished the carbonic acid in the plasma and disturbed the usual ratio of free carbon dioxide: combined carbon dioxide on which the hydrogen-ion concentration of the blood depends. The changes noted as a result of hyperpnea were an increase in p_H , a fall in plasma and alveolar carbon dioxide, and a cloudy alkaline urine, with a decrease in ammonia and titratable acid. Some of these results confirm earlier investigations.²⁵

We have laid emphasis heretofore on ionic equilibrium other than the hydrogen ion: hydroxide ion ratio, because, in the instance of parathyroid tetany, the concentration of calcium was markedly decreased, whereas, the acid-base equilibrium, as determined by hydrogen-ion potentiometer readings and by estimations of the plasma content and capacity of carbon dioxide, was not essentially disturbed;²⁶ and because, in gastric tetany, the normal relationship of anions was deranged, and the noted rise in p_H we erroneously believed to be insignificant.⁹ The findings in parathyroidectomized dogs need reinvestigation. MacCallum⁷ and Togawa²⁷ got results very similar to our carbon dioxide values; whereas McCann⁸ found a high carbon dioxide capacity after operation, and Howland and Marriott,²⁸ using the rather inaccurate dialysis-indicator method, corroborated our p_H findings, but Wilson's²⁹ conclusions were at variance. Wilson developed the alkalosis theory after measuring the equilibrium constant of oxyhemoglobin (i. e., Barcroft's K , the index of the oxygen capacity of hemoglobin solutions and a function of the hydrogen-ion concentration³⁰). It was found that after parathyroidectomy, the value of K rose. Wilson's results seemed to be fairly consistent, but the possibility was not ruled out that the marked disturbance of electrolytes which has been shown to occur after para-

24. Grant, S. B., and Goldman, A.: *Am. J. Physiol.* **52**:209 (June) 1920.

25. Davies, H. W.; Haldane, J. B. S., and Kennaway, E. L.: *J. Physiol.* **54**:32 (Aug. 19) 1920. Leathes, J. B.: *Brit. M. J.* **2**:165 (Aug. 9) 1919. Collip, J. B., and Backus, P. L.: *Am. J. Physiol.* **51**:568, 1920.

26. Hastings, A. B., and Murray, H. A., Jr.: Footnote 16, first reference.

27. Togawa, T.: *J. Lab. & Clin. Med.* **5**:299 (Feb.) 1920.

28. Howland, J., and Marriott, W. McK.: Footnote 18, first reference. Cushny, R.: *J. Physiol.* 391 (May) 1920.

29. Wilson, D. W.: Footnote 6, second reference.

30. Barcroft, J.: *The Respiratory Function of the Blood*, Cambridge. 1914.

case can be obtained in no other way. An electrometric method of measurement, similar in principle to that used for hydrogen determinations, which makes use of sodium and calcium amalgam electrodes has recently been introduced by Neuhausen and Marshall.³⁸ These investigators found that sodium ions and chlorid ions are present in the serum in approximately the same state of dissociation and activity as they are in a simple aqueous solution of sodium chlorid and that when the pressure of carbon dioxid is varied from 0 to 44 mm. of mercury, the concentration of free sodium ions rises from 1 to 2 per cent. at most. This result was interpreted by Neuhausen and Marshall to mean that the amount of sodium normally bound to protein, and freed, by increasing the acidity of the medium, is minimal. Determinations of calcium ion activity were less satisfactory, owing to difficulty with a very reactive amalgam electrode; but the results indicated that only about 10 per cent. of the calcium in serum is dissociated.

These conclusions seem to confirm the work of the German physiologists. However, there are these serious objections to accepting their conclusions: 1. The formula on which their theoretical considerations are based, namely, $[Ca] = \frac{k [H]}{[HCO_3]}$ is only true for a saturated solution of calcium carbonate, and therefore probably cannot be applied to plasma. 2. More recent researches to detect a change of dialysable calcium with varying carbon dioxid tensions gave negative results.³⁹ 3. The assumption that proteins combine more readily with calcium than with sodium has no experimental basis. 4. The assertion on which the entire theory depends, namely, that increasing base-proteinates decreases free calcium ions, is probably incorrect, since proteins ionize freely.

The foregoing paragraphs abstract in bare outline various researches which are relevant to the question of the etiology of tetany from the standpoint of the relative concentration of various electrolytes and the acid-base equilibrium in the blood. The significance of the anions (Cl^- , HCO_3^- , HPO_4^- , etc.) of the cations (Ca, Na, K, etc.) and of the p_H has been discussed. Our results and their bearing on the theories summarized will be reviewed after presentation of the case histories.

It is not to be thought that all possible hypotheses to explain this or other forms of tetany have been included. There are exhaustive investigations of experimental parathyroid tetany which point to the accumulation of large amounts of some toxic compound of nitrogen, believed to be methyl guanidin, as a cause, or at least an accompaniment, of

38. Neuhausen, B. S., and Marshall, E. K.: *J. Biol. Chem.* **53**:365 (Aug.) 1922.

39. Meysenberg, L. Von, and others: Footnote 34, second reference.

tany.⁴⁰ These findings have been verified in a few cases of infantile tetany⁴¹ and adult idiopathic tetany.⁴² As no studies have been made along these lines in gastric tetany, speculation at this time is idle. However, the fact that the injection of methyl guanidin will cause the calcium concentration of the blood to fall and tetany to ensue is of interest as pointing to a possible relationship between p_H , calcium activity and guanidin metabolism.⁴³

In our dogs, no convulsions in any way compared to the tetanic seizures after parathyroidectomy developed, and there was doubt at first that the condition known clinically as gastric tetany had been reproduced. It seems to us probable that the shivering, fibrillary twitchings, muscle spasms and clonic contractions which occurred to a greater or less extent in some of the animals on which operation was performed represent a condition comparable to tetany in human beings. In the first place, there is no evident reason why a convulsion should be selected as determinative of whether or not tetany is present in a dog; in fact, the spasms of the forelegs and feet which frequently come on after pyloric occlusion resemble the carpopedal spasms of human tetany more closely than the generalized convulsions seen after parathyroidectomy. Secondly, MacCallum tested the electrical irritability of the nerves after pyloric occlusion and found it markedly increased; particularly was the current necessary to produce a contraction with cathodal opening much diminished. This has been generally regarded as the most reliable test for tetany. Finally, in the cases to be reported, the dogs that developed unmistakable clinical tetany showed the same blood changes as the dogs that gave the above mentioned signs of hyperirritability.

It is concluded, then, that tetany can be produced in dogs by obstructing the pylorus; and that the operation causes certain chemical changes in the blood: (1) a rise in the carbon dioxid capacity of the plasma; (2) a fall in the chlorid content of whole blood and plasma; (3) an increased concentration of phosphorus and sulphur, and (4) a slight rise in p_H . The few blood analyses made for sodium and calcium were not decisive or consistent enough to be reported with any assurance.

40. Paton, D. N., and Findlay, L.: *Quart. J. Exper. Physiol.* **10**:203, 1916; *ibid.* **11**:1:77 (Mar. 1) 1917.

41. Burns, D., and Sharpe, J. S.: *Quart. J. Exper. Physiol.* **10**:345, 1916.

42. Findlay, L., and Sharpe, J. S.: *Quart. J. Med.* **13**:433 (July) 1920. Natrass, F. J., and Sharpe, J. S.: *Brit. M. J.* **2**:238 (Aug. 13) 1921. Koch, W. F.: *J. Biol. Chem.* **12**:313, 1912; **15**:43, 1913.

43. Watanabe, C. K.: *J. Biol. Chem.* **35**:553, 1918; **36**:531, 1918.

In the cases⁴⁴ studied, interest was centered on the carbon dioxid and chlorid concentrations of the blood. Subjects with a carbon dioxid tension of 70 per cent. by volume or over, or with a chlorid concentration below 5.5 gm. per liter for plasma or 4.3 gm. per liter for whole blood, were considered abnormal, and so were included in the group. The urea estimations were made routinely at first, but later, when these appeared to be invariably high, interest was aroused and, in a few cases, the other nitrogen fractions were also determined. The urea, uric acid and creatinin of the blood have been shown to be increased in cases of acute intestinal obstruction, but no study has been made of these substances after pyloric occlusion. Parts of the histories have been omitted as inconsequential to the main subject.

REPORT OF CASES

CASE 1.—History.—P. K., aged 71 years, Irish, a retired policeman, admitted, Feb. 8, 1922, complained of persistent vomiting of from three to four weeks' duration. At first, the vomiting followed taking of food, but later it became almost incessant, in small amounts at a time. On three occasions, he had abdominal pain localized in the left epigastrium; in each instance, it was dull, did not radiate and came on after eating. He was very constipated, the bowels moving only after salts were given, and then variably (patient thought about six times in the preceding three weeks). The urine had become scanty. The patient was always thirsty and at times hungry, but he could retain nothing. During the last year, he had lost about 80 pounds (36.3 kg.). Cardiac, respiratory, genito-urinary and nervous histories were essentially negative.

Examination.—The patient was a dyspneic, cyanotic, emaciated man of dull mentality, evidently acutely ill. Loss of subcutaneous fat, emaciation, diminution of tissue turgor and signs of dehydration, were evident. There was a feeble pulse and distant heart sounds. The apex beat was not felt, and the borders could not be percussed with surety on account of an overlying hyper-resonant lung. The patient had a barrel-shaped chest with prominent flaring costal margins, and prolonged expirations indicated emphysema. There were râles at both bases. The abdomen was flat. There was no distention and no gas. The abdominal wall was quite thick, but a mass seemed to be just palpable in the left epigastrium. Carcinoma of the stomach with stenosis of the pylorus was diagnosed.

February 8: The arterial sounds were practically inaudible. The systolic pressure seemed to be between 70 and 95. The diastolic pressure was not obtained. The plasma carbon dioxid capacity was 68.1 per cent. by volume. The vomitus and stool gave positive guaiac reactions for blood. The patient was given a glucose infusion (3,000 c.c.).

44. With one exception, the patients included in this group were treated in the surgical wards of the Presbyterian Hospital. I wish to thank Prof. Allen O. Whipple for his direction and encouragement. Most of the chemical analyses were made by Miss Chudnoff and Miss Kurland in the laboratories of the Hospital. Dr. Baumann initiated investigation in several cases and gave much practical assistance.

45. A short summary of the series was read before the Society for Experimental Biology and Medicine, Proc. Soc. Exper. Biol. & Med. **19**:273, 1922.

Case	Diagnosis	Volume and Date	Duration of Illness	Examination										Examination of Stomach Contents	Examination of Urine	Examination of Blood	Examination of Sputum
				General	Local	Stomach	Rectum	Genitals	Excretory	Excretory	Excretory	Excretory	Excretory				
1. S.	Carcinoma of stomach	100 cc	10 days	General: Good	Local: Good	Stomach: Good	Rectum: Good	Genitals: Good	Excretory: Good	Excretory: Good	Excretory: Good	Excretory: Good	Excretory: Good				
2. S.	Carcinoma of stomach	100 cc	10 days	General: Good	Local: Good	Stomach: Good	Rectum: Good	Genitals: Good	Excretory: Good	Excretory: Good	Excretory: Good	Excretory: Good	Excretory: Good				
3. S.	Carcinoma of stomach	100 cc	10 days	General: Good	Local: Good	Stomach: Good	Rectum: Good	Genitals: Good	Excretory: Good	Excretory: Good	Excretory: Good	Excretory: Good	Excretory: Good				
4. M.	Carcinoma of stomach	100 cc	10 days	General: Good	Local: Good	Stomach: Good	Rectum: Good	Genitals: Good	Excretory: Good	Excretory: Good	Excretory: Good	Excretory: Good	Excretory: Good				
5. M.	Carcinoma of stomach	100 cc	10 days	General: Good	Local: Good	Stomach: Good	Rectum: Good	Genitals: Good	Excretory: Good	Excretory: Good	Excretory: Good	Excretory: Good	Excretory: Good				
6. M.	Carcinoma of stomach	100 cc	10 days	General: Good	Local: Good	Stomach: Good	Rectum: Good	Genitals: Good	Excretory: Good	Excretory: Good	Excretory: Good	Excretory: Good	Excretory: Good				
7. E. L.	Carcinoma of stomach	100 cc	10 days	General: Good	Local: Good	Stomach: Good	Rectum: Good	Genitals: Good	Excretory: Good	Excretory: Good	Excretory: Good	Excretory: Good	Excretory: Good				

* The concentration of carbon dioxide is given in percentage by volume; of chlorid in grains per liter; of urea, creatinin, nonprotein nitrogen and uric acid in milligrams per hundred cubic centimeters. Chlorid values are for whole blood except in Cases 3 and 4, and in the lowest reading in Case 5. In Cases 3, 4 and 5, the plasma was used.

February 9: Blood examination showed: hemoglobin, 95 per cent.; red blood count, 6,560,000; white blood count, 23,800; polymorphonuclears, 86 per cent. A glucose hypodermoclysis (5,500 c.c.) was given through six needles simultaneously. Roentgen-ray examination of the stomach after a barium sulphate meal showed complete obstruction, with no peristaltic waves evident. The lesser curvature showed an irregular outline. The pylorus did not fill.

February 10: The blood pressure was 72 systolic, 34 diastolic. The plasma carbon dioxid capacity was 70 per cent. by volume; the whole blood chlorids amounted to 4.34 gm. per liter; the nonprotein nitrogen was 1.33 gm. per liter, and urea to 1.52 gm. per liter. The Wassermann test was negative with both antigens.

February 13: Since entrance, the patient had been almost semicomatose, with a few lucid moments and occasional periods of restlessness and irrationality. He was incontinent, so it had not been possible to collect urine specimens previously. The reaction of the specimen obtained was neutral. There were no casts and no albumin. The plasma carbon dioxid capacity was 23.4 per cent. by volume.

During the last three days, the patient was given hypodermoclyses to maintain his fluid intake. Gastric lavage was carried out several times, food and barium sulphate ingested three or more days previously being recovered. Despite colonic irrigations, enemas and administration of cathartics through the stomach tube, complete obstipation persisted. There were no signs of intestinal contents in the returns from gastric lavage, and there was no abdominal distention, so that it seemed fair to assume that there was a practically complete obstruction at the pylorus.

February 14: The plasma carbon dioxid capacity was 21.2 per cent. by volume. The urine was again neutral, showing no casts and no albumin. A large abscess, apparently from a tooth, developed in the submaxillary region on the left side. Vomiting became incessant. Operation was considered inadvisable because of the manifold complications and patient's poor general condition, efforts to improve which had been unavailing; and because it seemed almost certain that there was present an incurable carcinoma of the stomach.

February 16: The patient died. Necropsy was refused.

In this case, although there was no verifying operation or necropsy, pyloric obstruction seemed certain, probably due to carcinoma. As in the other cases, the carbon dioxid capacity and the concentration of the protein metabolites were increased in the blood. The chlorids were a little low despite the fact that, the previous day, the patient had received over 5 liters of sodium chlorid, subcutaneously. Near the end of the illness, the carbon dioxid content changed rather suddenly from a high to a low figure, possibly owing to a terminal nephritis with acidosis. This sudden reversal of an abnormality in blood reaction was noticed in two of our dogs at the approach of death. Owing to the patient's incontinence, frequent tests could not be made of the urine, but the two specimens examined were neutral in reaction and were negative for albumin and casts. No symptoms of tetany developed.

CASE 2.—*History*.—M. S., aged 52 years, an American housewife, entered the hospital, July 23, 1921, complaining of vomiting continuing over a period of four months. Up to six months previously the patient said, she had been quite

well. Suddenly one morning, without any apparent cause, she became nauseated and vomited her breakfast. She had no more trouble for a month, and then suffered a similar attack. There was an accompanying sense of pressure in the epigastrium, but no real pain. The patient said that, for the four months previous to admission, these periodic attacks of nausea and vomiting had been increasing in frequency. She often vomited food which she had eaten twenty-four hours previously. For a week before examination, she had vomited every day. Vomiting relieved the sense of fullness at first, and later the dull, twisting pain which, occasionally developed. If she did not eat, she did not suffer. The pain, although not severe, became continuous, and she entered the hospital in a very weakened condition. She had noticed "bunches in the upper abdomen" moving across from left to right. She became more and more constipated. There had been a loss of from 20 to 30 pounds (9 to 13.5 kg.) in weight. The past history did not have any apparent bearing on the present condition. Family and personal histories were irrelevant.

Examination.—The patient was of poor physique, with evidences of loss of flesh. The sclera and cornea of the right eye were scarred, and the patient was blind in this eye (old injury). Carious teeth; coated tongue, with fine tremor, and easily palpable and tortuous arterial walls were noted. Abdominal examination disclosed a narrow costal angle, a sense of a mass near the midline, a slow peristaltic wave moving from left to right in the umbilical region, and kidneys palpable on both sides. The opinion on entrance was that the patient was suffering from chronic ileus, which was probably caused by a malignant growth of the colon. Examination of the blood revealed: blood urea, 58 mg. per hundred cubic centimeters; uric acid, 3.1 mg. per hundred cubic centimeters; chlorids, 3.75 gm. per liter and carbon dioxid, 67.1 per cent. by volume. Four days later, the blood urea was 54 mg. per hundred cubic centimeters; chlorids were 3.5 gm. per liter, and carbon dioxid capacity was 63.6 per cent. by volume. The blood Wassermann reaction was + + + + with both antigens on two examinations. The spinal fluid Wassermann reaction was negative. The roentgen-ray examination of the gastro-intestinal tract, six hours after a barium sulphate meal, showed a large atonic stomach without evidence of peristalsis. The duodenum, which seemed to be fixed, was deflected to the right; twenty-four hours after eating, the largest amount of the meal was in the rectum; the rest was in the cecum and splenic flexure. Roentgenograms and fluoroscopy of the colon after a barium sulphate enema did not reveal any abnormalities.

August 3: The analysis of a specimen of vomitus revealed free hydrochloric acid, 0; total hydrochloric acid, 20 per cent. These figures were confirmed by examination of an extracted sample. The patient underwent lavage frequently during the period of observation. The urine was always acid and at two out of four examinations showed albumin +. The patient received two infusions of 3 per cent sodium chlorid solution, after which the blood chlorid concentration was 4.2 gm. per liter. The preoperative diagnosis was difficult, the main points being (1) age (52 years); (2) a history of four months' of vomiting without any real pain; (3) a loss of from 20 to 30 pounds (9 to 13.5 kg.); (4) a four plus Wassermann reaction; (5) hypochloremia, with a slightly elevated carbon dioxid; (6) roentgen-ray evidence of gastric dilatation and atony with pyloric or duodenal obstruction; (7) marked visible peristalsis, which was believed to be in the transverse colon; (8) negative roentgen-ray examination of the colon.

Operation (Dr. St. John).—August 3: Partial enterectomy (jejunum), was performed, with end to side anastomosis. When the abdominal cavity was

opened, markedly distended and thickened loops of proximal jejunum presented. About 8 to 10 feet below the duodenojejunal angle, there was a pronounced constriction, caused by dense white scar tissue. Below this constriction, the intestines were shrunken and appeared like a flattened ribbon. The constricted portion was excised, and an end to side anastomosis was performed. A rubber tube was inserted in the distended jejunum above the anastomosis and held with a purse string suture. Microscopic examination of the specimen revealed irregular masses of atypical glandular cells. Carcinoma of the jejunum was diagnosed.

Course.—Recovery was rapid.

August 4: The blood chlorids were 5.3 gm. per liter.

August 5: The blood urea was 82 mg. per hundred cubic centimeters and the chlorids were 4.9 gm. per liter. The patient was apathetic and drowsy but was easily aroused. She was fed with glucose solution through the jejunal tube.

August 6: The blood urea was 80 mg., plasma carbon dioxid, 73 per cent. by volume, and blood sugar 1.35 gm. per liter.

August 8: The patient was still stuporous. An enormous discharge occurred through the intestinal tube, which was then removed and the abdomen exposed to the air under an electric bake. The patient was instructed to keep the skin clean with gauze. The blood urea was 37 mg. per hundred cubic centimeters and plasma carbon dioxid, 71.1 per cent. by volume. The patient had a mild post-operative psychosis. She seemed in a semistupor and spoke only in a whisper, with words run together in a monotone. She made unusual grimaces and showed the "catatonic" phenomenon; i. e., spastic extremities yielding slowly to pressure and remaining as placed.

August 9: The urine was alkaline and showed a faint trace of albumin.

August 12: The blood urea was 40 mg. per hundred cubic centimeters, the chlorids were 4.8 gm., and the plasma carbon dioxid was 50.4 per cent. by volume. The wound was dressed every day, the discharge became gradually less and granulations slowly closed the sinus.

September 10: The blood urea was 31 mg. per hundred cubic centimeters, the chlorids were 5.4 gm. per liter and the carbon dioxid was 64.2 per cent. by volume. In five out of seven examinations of urine after operation, the reaction was acid and tests showed albumin twice.

September 12: The patient was discharged, improved.

Thirteen months after operation, the patient was seen in the follow-up clinic. She looked well and said she had no symptoms.

The preceding case is an interesting one for a number of reasons, all of which are not relevant to the subject matter of this article. From a chemical standpoint, it is worthy of note that this case is different not only as regards the position of the occlusion—it is the only case of the series in which the obstruction was not at the pylorus—but also as regards the relative change in bicarbonate and chlorids. It will be noted that, although the chlorids were markedly decreased before operation, the carbon dioxid was not elevated beyond a high normal. The possibility of using this relationship as a point of diagnosis for determining the location of the obstruction is worth considering. In other words, hypochloremia will be found in all cases of persistent vomiting, but alkalosis will be present only when there is a greater amount of

and plasma chlorid, 4.6 gm. per liter, in case of an obstruction near the pylorus. The urine was for the most part acid, and only occasionally gave a positive flame test for albumin, but the urea concentration of the blood was elevated. It may be significant to note that, in this case as well as in others, the urea which was found increased before operation rose still higher for a few days after operation, and later descended to within normal limits.

CASE 3.—History.—J. S., aged 57 years, an Italian laborer, entered the hospital, March 23, 1921, with the typical signs and a history of acute appendicitis of twenty-one hours' duration, with pain, tenderness, spasm and a mass in right lower quadrant. Vomiting was minimal.

Operation.—At the emergency operation (appendicectomy with drainage), a gangrenous appendix, with localized peritonitis was found. The anesthesia was commenced with 0.5 per cent procain, but after the peritoneal cavity was opened, gas-oxygen was used.

Course.—The immediate postoperative recovery was satisfactory, but two days later the patient developed distention of the stomach.

March 26: Gastric lavage with warm 5 per cent. sodium bicarbonate solution was administered. Later, the patient received 1,000 c.c. of 10 per cent. glucose, intravenously. During the next four days, on account of recurring dilatation the patient was given lavage seven times. In that time, he also received five glucose infusions. Moderate amounts of turbid fluid and much gas were recovered at each lavage. At one time, 1½ ounces of castor oil was introduced through the stomach tube, with the hope of remedying what seemed to be a general atony of the entire gastro-intestinal tract. Enemas and colon irrigations were employed for the same purpose. The abdominal wound was treated with surgical solution of chlorinated soda (Dakin's solution), according to a modified Rulison technic. Drainage seemed to be adequate.

April 1: The patient seemed better. There was no distention and no vomiting. The last gastric lavage had brought away only clear fluid. Blood analysis revealed: plasma carbon dioxid, 86.2 per cent. by volume; urea, 97 mg. per hundred cubic centimeters; creatinin, 1.8 mg. per hundred cubic centimeters. Slight twitchings were noted in the extremities, but no real carpopedal

April 2: The following concentrations were determined in the blood: plasma dioxid, 82 per cent. by volume; urea, 80 mg. per hundred cubic centimeters; creatinin, 1.89 mg. per hundred cubic centimeters; uric acid, 8 mg.; chlorid, 4.6 gm. per liter. The general condition of the patient was the same. There was no longer occasion for gastric lavage.

April 3: The patient had four bowel movements. He seemed to be much better. The wound was healing satisfactorily.

April 4: Chemical tests showed: plasma carbon dioxid, 82.4 per cent. by volume; urea, 110 mg. per hundred cubic centimeters; creatinin, 2.2 mg. per hundred cubic centimeters; uric acid, 7.5 mg., and plasma chlorids, 4.5 gm. per liter.

April 5: The concentration of calcium in the plasma was 10 mg. per hundred cubic centimeters.

April 6: The patient did not appear to be so well. He seemed unresponsive, tired and sleepy. He complained of anorexia and buzzing in the ears. Blood analysis showed: plasma, 76.6 per cent. by volume; urea, 40 mg. per hundred

cubic centimeters; uric acid, 2.6 mg., and chlorids, 5.1 gm. per liter. The urine diminished in quantity. The urine had been, and still was, consistently negative except on one occasion, when albumin and casts were noted. The reaction was always acid. The next day the patient felt much better, however, and improved rapidly thereafter.

April 8-9: The nitrogen intake was approximately 9.3 gm., the excretion 14.42 gm.

April 13: The phenolsulphonephthalein test showed 35 per cent. in two hours.

April 15: There was an unusually large urinary output. No more signs of renal insufficiency developed.

April 27: The patient was discharged, improved.

This was a case in which, in the course of convalescence from an operation for acute appendicitis, general gastro-intestinal paralysis developed. It was most conspicuous in the stomach, which became recurrently distended. Lavages were regularly resorted to, with considerable temporary relief. About one week after operation, chemical examination of the blood disclosed that the carbon dioxid, urea and uric acid concentrations were increased, and the plasma chlorids were subnormal, but the creatinin content, which is considered by some the most delicate test for pathologic conditions in the kidney, was within the usual limits. The patient did not have tetany, but he showed the hemic changes, though in a less degree, that occurred in other patients who did develop tetany. It is impossible to separate the gastric element and the possible effect of the paralytic ileus. We should be inclined to include this case in the series because of the high carbon dioxid (86.2 per cent. by volume), which would be an indication that hydrochloric acid had been removed. This is consistent with the idea that there exists in gastric dilatation a spasm of the pylorus, with relaxation of the body. Thus, the secreted hydrochloric acid, becoming stagnant in a dilated stomach instead of passing on into the intestines for reabsorption, is finally lost to the body through vomiting or by gastric lavage. The interference with the passage of hydrochloric acid limits the usual initiating stimulus to pancreatic secretion, and thus the abstraction of hydroxyl ions from the blood which otherwise would compensate for the hydrogen ions lost. Of course, we cannot feel sure that this view is correct.

CASE 4.—*History.* T. M., aged 46 years, tall & well-developed, entered hospital, May 27, 1921, complaining principally of persistent vomiting of one month's duration. He said that ten years previously he began suffering from indigestion in the form of epigastric distress after meals, belching and occasional vomiting. He had always been constipated. For many years, he had indulged regularly in alcohol. During the previous year, he had been bothered with epigastric pain, which was relieved somewhat by eating. One month ago, while on his beat, he suddenly vomited many times after an attack of sudden severe epigastric pain. Since that day, he had been unable to retain anything

on his stomach. During the last month, he had lost about 50 pounds (22.7 kg.) in weight. The family history was of no importance. There was a history of headaches, dizziness with fainting, failing eyesight and precordial pain. The patient said that he had a chancre thirty years previously. The urinary history was negative.

Examination.—The patient was a large framed, corpulent man of florid complexion. He showed loss of weight, but looked healthy. The arteries were tortuous. There was a transmitted systolic murmur at the apex. A slight cyanotic tinge of the mucous membranes was evident. The blood pressure was 158 systolic, 74 diastolic. The liver edge could just be felt. Otherwise, the abdominal examination was negative. There were no masses and no points of special tenderness. Ulcer of the stomach with stenosis of the pylorus was diagnosed. Roentgen-ray examination, six hours after the ingestion of barium sulphate, showed that none of the meal had passed through the pylorus; but the twenty-four hour plate showed that the stomach was empty. The Wassermann test was negative with both antigens. The analysis of the gastric contents showed free hydrochloric acid, 10 per cent., and total acid, 35 per cent.

May 28: The patient felt quite weak. He said that earlier in the morning he had had spasms in his fingers so that he could not straighten them. He was given an infusion of physiologic sodium chlorid solution. Before the infusion, blood tests showed plasma carbon dioxid capacity, 80.6 per cent by volume; plasma chlorids, 4.7 gm. per liter; plasma phosphates, 5 mg. per hundred cubic centimeters; urea, 105 mg. per hundred cubic centimeters. After the infusion, the tests showed: plasma carbon dioxid capacity, 80.6 per cent. by volume; plasma chlorids, 5.09 gm. per liter; plasma phosphates, 4.5 mg. per hundred cubic centimeters; urea, 101 mg. per hundred cubic centimeters. The urine was acid and showed no albumin and no casts. Gastric lavage was performed twice, with the return of large amounts of fluid and food residue.

May 29: The patient was given a gastric lavage, a hypodermoclysis and an infusion of 1.7 per cent. sodium chlorid solution in 10 per cent. glucose. Before the infusion, the plasma carbon dioxid was 76.8 per cent. by volume. After the infusion, it was 73.0 per cent. by volume.

Operation.—May 30: Exploratory celiotomy, with posterior gastro-enterostomy was performed by Dr. Whipple. Examination revealed a very large indurated mass in the region of the pylorus adherent to the pancreas and the portal fissure. It was so tightly adherent that the removal of it was considered out of the question because of the patient's condition and the danger to vital structures, particularly the portal vein. There did not appear to be any hard glands indicative of carcinoma, and it was thought best to perform only a posterior gastro-enterostomy to relieve obstruction. Microscopic examination of some involved tissue from near the site of the ulcer showed no evidence of new growth.

Course.—After the operation, the patient was very sick and for two weeks downhill steadily. He finally recovered in a dramatic fashion. He was treated by daily infusions and hypodermoclyses to maintain normal fluid content, and by gastric lavages for distention, vomiting and gastric retention.

May 31: The plasma carbon dioxid capacity was 59.8 per cent. by volume; plasma chlorids amounted to 5.38 gm. per liter; sugar, 1.17 gm. per liter; urea, 110 mg. per hundred cubic centimeters. The patient was then given an infusion (1,000 c.c.) of 10 per cent. glucose. The blood tests were then repeated. Plasma carbon dioxid capacity, 67.5 per cent. by volume; plasma

chlorids, 5.38 gm. per liter; sugar, 6.5 gm. per liter; urea, 109 mg. per hundred cubic centimeters. During the next few days, the patient continued to vomit, so that oral feeding was impossible.

June 6: Roentgen-ray and fluoroscopic examinations showed that the gastro-enterostomy stoma was open and functioning, and, as the patient's bowels moved regularly, he was often incontinent. It was thought that the vomiting could not be explained on the basis of an obstruction.

June 8: Blood tests showed: plasma carbon dioxid capacity, 40.9 per cent. by volume; plasma chlorids, 5.16 gm. per liter; urea, 230 mg. per hundred cubic centimeters; uric acid, 14.5 mg. per hundred cubic centimeters; creatinin, 3.8 mg. per hundred cubic centimeters.

June 9: Phenolsulphonephthalein excretion was 22 per cent. in two hours.

June 11: The plasma carbon dioxid capacity was 44.7 per cent. by volume; urea, 191 mg. per hundred cubic centimeters; creatinin, 2.8 mg. per hundred cubic centimeters. The patient became drowsy and stuporous and at times irrational. He was evidently losing ground. Gastric lavages were necessary for the retention, hiccuping and recurrent dilatation.

June 14: The plasma carbon dioxid capacity was 40.9 per cent. by volume; urea, 167 mg. per hundred cubic centimeters; creatinin, 1.75 mg. per hundred cubic centimeters. The blood pressure was 75 systolic, 50 diastolic, and the heart sounds were poor. The patient was then given digitalis in rather large doses through the stomach tube. This seemed to be the turning point and in two days the man was transformed from a condition of semicoma with dyspnea and cyanosis to the convalescent state. Improvement was rapid.

June 22: The plasma carbon dioxid capacity was 55.1 per cent. by volume; urea, 142 mg. per hundred cubic centimeters; uric acid, 2.3 mg. per hundred cubic centimeters.

July 9: The patient was discharged, improved.

The chief interest in this case was the remarkable rise and the gradual fall in the protein metabolites. Nine days after the operation, the values for urea, uric acid and creatinin were near a fatal level prognostically, with a low carbon dioxid capacity; two weeks later, the concentration figures were normal. Before the operation, the man had a mild alkalosis and reported spasms of the fingers, but no signs of tetany were demonstrable.

CASE 5.⁴⁶—*History*.—J. O. W., aged 28 years, an American, entered, March 3, 1921, complaining of vomiting of about two months' duration. He first noticed that he had a "sour stomach," but soon afterward began to have spells of vomiting. These were preceded by a feeling of fulness and distress. The vomitus was enormous in amount, sour and frothy, and contained undigested food. Vomiting increased in frequency, finally occurring once a day. The patient also complained of eructations, flatulence and nausea after meals. The appetite had been poor, and the bowels constipated. He said he had never had pain in the epigastrium. The average weight was 185 pounds (84 kg.). Weight on admission was 137 pounds (62 kg.). Nothing relevant was learned from the family or personal history.

46. This case from the medical service of the Johns Hopkins Hospital is published with the kind permission of Dr. Longcope.

Examination.—The patient was quite thin, and flabbiness of the skin gave evidence of loss of weight. The right pupil was larger than the left, the tongue was thickly coated and there was pyorrhea. The heart and lungs were negative. The abdomen was slightly scaphoid. The liver edge was not felt. There was some resistance in the epigastrium. The stomach on percussion seemed to be markedly distended.

March 4: A rice and raisin meal was given the patient in the evening, but he vomited 1,200 c.c. early the next morning. The vomitus showed rice and raisins. The guaiac test was strongly positive. The blood Wassermann reaction was negative. In a phenolsulphonephthalein test, after one hour the urine (10 c.c.) showed 10 per cent.; after the second hour, the urine (35 c.c.) showed 37.5 per cent.; total, 47.5 per cent. Roentgen-ray examination of the gastrointestinal tract showed a wedge-shaped filling defect of the pylorus and a cow-horn shaped stomach, moderately ptosed. Peristalsis of the dilated stomach was very active, but no barium sulphate passed the pylorus, which seemed to be obstructed. There was no occult blood in the stool. The blood count showed: erythrocytes, 5,840,000; hemoglobin, 115 per cent.; leukocytes, 8,400. The blood pressure was 130 systolic and 80 diastolic. The specific gravity of the urine was 1.045. It was acid, and showed a faint trace of albumin, casts and a large amount of acetone.

March 7: The patient was able to retain very little by mouth. During a gastric lavage, he complained of cramps in his arms and feet, and, about five minutes later, he had a generalized tetanic convulsion. There was no loss of consciousness, and for a period of about five minutes, while the attack lasted, he seemed to suffer a great deal. About ten minutes after the convulsion, the signs of Trousseau and Chvostek were present.

March 8: The p_{H} was 7.42. The plasma carbon dioxid capacity was 103 per cent. by volume. The plasma chlorids amounted to 3.67 gm. per liter. The freezing point depression was 0.524 degrees (normal, about 0.54 degrees). The protein calculated from the refractive index was 8.9 per cent. and by the Kjeldahl method, 8.4 per cent. Other measurements were: specific conductivity, 96.9 (normal about 120); plasma sugar, 143 mg. per hundred cubic centimeters; nonprotein nitrogen, 82.2 mg. per hundred cubic centimeters; calcium, 10.8 mg. per hundred cubic centimeters; potassium, 20 mg. per hundred cubic centimeters; sodium, 282 mg. per hundred cubic centimeters. The urine contained a large amount of acetone.

Operation.—March 11: Pylorotomy with posterior gastro-enterostomy was performed. An old pyloric ulcer with a dense band of connective tissue was found, causing marked obstruction. The microscopic examination of the specimen showed carcinoma. The patient's immediate convalescence from operation was smooth. He took fluid and food well, and made no complaint. Suddenly, March 19, he began to talk irrationally and incessantly; he was disoriented as to time and place, and could not recall names of physicians or nurses. Later, he had hallucinations and delusions. Temperature, pulse and respirations were normal.

March 22: Plasma carbon dioxid capacity was 58.7 per cent. by volume.

March 23: The optic disks were a little indistinct and there were several fresh hemorrhages on both sides. The blood urea nitrogen was 22.7 mg. per hundred cubic centimeters; the nonprotein nitrogen, 55.5 mg. per hundred cubic centimeters; and the plasma chlorids amounted to 6.3 gm. per liter. Urinary examination showed albumin (a trace) many casts and a few leukocytes. The blood pressure was 110 systolic and 70 diastolic.

The rest of the patient's convalescence was marked by the development of a psychosis, but in all other respects his condition was excellent, and when dismissed, April 15, he could eat freely of a liberal diet. Six months later word was received from the family physician that the patient, had died, presumably from carcinomatosis.

This was a typical case, with definite signs of clinical tetany and marked changes in the blood. The one p_H estimation made was within the normal range, but the concentration of carbon dioxid was over 100 per cent. by volume and the protein catabolites above normal. The sodium was low. A particularly interesting finding was the very low figure for the specific conductivity of the serum which was about 20 per cent. subnormal.

CASE 6.—History and Examination.—J. McA., aged 41 years, an Irish laborer, entered the hospital, June 23, 1920, with a typical history of acute appendicitis. Physical examination showed tenderness, rigidity and a small mass in the right lower quadrant. The patient told of ten years of epigastric pain radiating through to the back, coming on two hours after meals, relieved by bending over and by ingestion of sodium bicarbonate. This was suggestive of a pyloric ulcer. The Wassermann test was negative.

Operation.—An emergency operation was performed through a MacBurney incision, which revealed a gangrenous appendix and spreading peritonitis. The upper abdomen was not explored. The diseased area was drained by two rubber tubes.

Course.—The patient had a stormy convalescence. At first, he had difficulty in voiding.

June 29: He vomited blood.

July 1: He passed a tarry stool, and vomited more blood. It was believed that an ulcer, presumably of the pylorus, had commenced bleeding. The patient's outward condition seemed satisfactory, and the wound was healing rapidly. During the first week, the urine was acid and showed a trace of albumin in two out of three examinations.

July 8: A gastric lavage was given, with a return of brown fluid resembling old blood.

July 10: Analysis of the contents after a gastric lavage showed: free hydrochloric acid, 16; total acid, 42.0; guaiac test, positive. A blood count showed: erythrocytes, 3,346,000; hemoglobin, 65 per cent.

July 21: The sinus was healed and the patient was considered to have recovered from appendicitis. A roentgen-ray and fluoroscopic examination after a barium sulphate meal revealed marked retention in the stomach, but not a complete obstruction and no duodenal deformity. With a tentative diagnosis of duodenal ulcer, the patient was transferred to the medical division for treatment, under a careful dietary regimen.

July 23: The urine was alkaline to litmus. There was a trace of albumin. Analysis of the gastric contents after a serial test meal showed: free hydrochloric acid, 4 to 40; total acid, 14 to 72; guaiac test, positive. A guaiac test on a stool was also positive. For the next three days, the patient vomited steadily, despite withdrawal of a soft diet.

July 26: A blood count showed: erythrocytes, 2,920,000; hemoglobin, 50 per cent.

July 27: The stool was guaiac positive. The urine was acid and the microscopic examination revealed albumin and casts. The plasma carbon dioxide capacity was over 100 per cent. by volume.

July 28: The plasma carbon dioxide capacity was 104 per cent. by volume. The patient's condition was poor. He vomited once during the night. He seemed lethargic and weak. Breathing was quiet. Marked muscular hyperirritability was noted. Chvostek's sign was positive on the right side. He was thought to be suffering from mild tetany. No definite carpopedal spasm was present, and Trousseau's sign was negative.

July 29: A transfusion was given. The operation which was to follow was cancelled on account of a severe transfusion reaction. The patient became much worse. Respirations were slow and irregular; the pulse rapid and of low tension. Typical facial spasm and twitchings were noted. In the afternoon, he became comatose; the respirations dropped to about seven per minute, and the mucous membranes became cyanosed. The plasma carbon dioxide capacity was 86 per cent. by volume. An infusion of 900 c.c. of saline, 500 c.c. of 10 per cent. glucose, 1 c.c. of epinephrin and 12 c.c. of tenth normal hydrochloric acid was given. After the infusion, the plasma carbon dioxide was 64 per cent. by volume. There seemed to be some slight improvement in the general condition, but consciousness did not return.

July 29: A liter infusion of 10 per cent. glucose, 10 minims of epinephrin, and 3 c.c. of tenth normal hydrochloric acid was given.

July 30: The patient died. Request for necropsy was not granted.

The diagnosis of duodenal ulcer with pyloric stenosis was almost certain in this case. The patient gave a typical history. The roentgen-ray examination and the repeated finding of blood in the stool and vomitus completed the evidence. Tetany, which finally developed, was preceded by the gradually developing signs of pyloric obstruction; vomiting was frequent, and numerous gastric lavages were given. At the time of the appearance of muscular hyperirritability, facial twitchings and Chvostek's sign, on which the diagnosis of tetany was made, the plasma carbon dioxide capacity was 104 per cent. by volume. The chlorids were not determined. At the end of the illness, when the patient was practically comatose, infusions were administered, two of which contained minute amounts of hydrochloric acid (i. e., in concentrations of 0.0008 and 0.0003 normal, respectively). Even this infinitesimal amount was given with some trepidation, and, of course, the dosage was far too small to produce a therapeutic effect. Unfortunately, the urea concentration of the blood was not tested, but the presence of albumin and casts in the urine suggests that, as in the other cases, a rise in urea might have been anticipated. It is easy to say now, in retrospect, that the temporizing policy adopted was unfortunate, when a simple gastro-enterostomy under local anesthesia might have prevented the onset of tetany and saved the patient's life. The decision was made difficult at the time by the fact that these fatal symptoms of pyloric obstruction were developing during the period of convalescence from an operation for acute appendicitis with peritonitis; that

severe bleeding from the ulcer had resulted in a secondary anemia, thus lowering the patient's general resistance to any operative procedure, and that careful dietary regulation had once been successful and had brought him well along the road to recovery at an earlier period of his convalescence.

CASE 7.—History.—E. L., aged 62 years, an American housewife, entered the hospital as a private patient, February 17, 1922, complaining chiefly of upper abdominal pain of five months' duration. She said that in the beginning the pain came on about one-half hour after meals, and usually lasted for about an hour. It was relieved by bismuth and bicarbonate of soda, and by lying down. It was aggravated by eating. On entrance, the pain had become continuous and of a dull burning character. After meals, it often became knife-like. It was then rather definitely localizable on the right side of the abdomen at the umbilical level. With the pain, there had been some distention and gaseous eructations. The patient had been vomiting lately (extent and duration not recorded) and had lost about 13 pounds (about 6 kg.) in weight. The patient had been remarkably free of symptoms referable to the cardiovascular, respiratory, genito-urinary or nervous system. Her physician reported that the symptoms of pyloric occlusion had been steadily becoming more apparent and that gastric lavage had demonstrated some retention. Analysis showed: free hydrochloric acid, 20; total acid, 38.

Examination.—The patient was a rather thin, nervous, woman, without any definite outward signs of disease or evident loss of weight. She had lost all but four teeth. The tongue was coated and the pharynx slightly injected, but there were no significant abnormalities of the head, neck or chest. In the right upper portion of the abdomen, there was a small, hard, freely movable mass about 6 by 4 cm., which descended with respirations and which was somewhat tender. A diagnosis of carcinoma of the stomach with stenosis of the pylorus was made. Blood examination showed: hemoglobin, 80 per cent.; erythrocytes, 4,700,000. The urine was acid. Tests for albumin, casts and glucose were negative. The blood pressure was 130 systolic, 80 diastolic.

Clinical Course.—February 17: Gastric lavage was performed, with a clear return only after 6 quarts (liters) had been used. The patient vomited once. For the next three days, i. e., up to the day of operation, the patient was given lavage once a day, in each case with the return of considerable material having the appearance of coffee grounds.

Operation.—February 21: Exploratory celiotomy and posterior gastro-enterostomy were performed by Dr. Whipple. Examination showed that the mass felt before operation was a large, freely movable carcinoma in the pyloric end of the stomach. There was lymphatic extension through the gastrohepatic omentum and over the surface of the pancreas. The lymph nodes of both lesser and greater curvature were involved, with typical metastatic nodules. Because of the extensive ramifications of the growth, a complete removal with pylorotomy was considered impossible. As a temporary relief for the pyloric obstruction, a posterior gastro-enterostomy was performed in the usual manner, with a short jejunal loop. The patient stood the operation well. Microscopic examination of a piece of tissue from near the head of the pancreas showed carcinoma, evidently from the stomach.

During the three days after operation, the patient received two transfusions, a glucose infusion and a saline hypodermoclysis to relieve thirst and evident

dehydration. Bileflow into the stomach, which was noticed before operation, recurred and marked gastric dilatation ensued, relieved somewhat by lavage, which was performed once or twice daily. Despite the large amounts of fluid administered, there was oliguria. The urine remained acid, and albumin and many hyaline and granular casts were noted.

February 25: Blood urea amounted to 2.47 gm. per liter, whole blood chlorids, 4.00 gm. per liter. The usual gastric lavage was given, and was repeated twice the following day.

February 27: Blood urea amounted to 3.34 gm. per liter; whole blood chlorids, 2.51 gm. per liter; total plasma carbon dioxid capacity was 107.6 per cent. by volume. The patient developed twitchings of the hands and arms, which some thought were a manifestation of uremia and others of tetany. She became confused and disoriented mentally. The tongue was brown and dry. Albumin and casts were plentiful, and once more the urine became scanty. At 8 p. m., the patient received an infusion of 1 liter of a solution made by mixing 500 c.c. of tenth normal hydrochloric acid with 500 c.c. of tenth normal sodium (physiologic sodium chlorid solution). The blood then showed: plasma carbon dioxid capacity, 86.2 per cent. by volume; whole blood chlorids, 3.31 gm. per liter. One hour after the infusion, the patient showed unmistakable carpopedal spasm. Spontaneously, she assumed the attitude pathognomonic of tetany. The nurse said that she had definitely noted the same phenomenon the previous night, but it was not observed during the day. Twitchings of the mouth and fibrillary contractions of the muscles of the extremities were almost constant.

February 28, at 1 a. m., the carpopedal spasms were no longer present, but continuous fibrillary twitchings very much like those seen in dogs with alkalosis were marked. At 9 a. m., the patient died.

This was a case of carcinoma of the stomach with pyloric obstruction in an elderly woman, with a history of vomiting. On the fifth day, after a palliative gastro-enterostomy, the blood urea and carbon dioxid were inordinately high, and the chlorids very low. The next day, tetany developed. Before operation, the kidneys were apparently not damaged (i. e., the urine showed no albumin, and no casts; the output was satisfactory; the blood pressure was normal, etc.), but after the operation, albumin and casts appeared, the urine became scanty and the blood urea was higher than normal. It is of interest to note that the urine was always acid despite the very high alkaline reserve in the blood. (No cases have been found in the literature with such a high figure for the carbon dioxid capacity.) The carbon dioxid was lowered and the chlorids were increased by an intravenous injection of 1 liter of twentieth-normal hydrochloric acid in a saline solution, with no apparent deleterious effects. The number of cubic centimeters of tenth-normal (0.365 per cent.) hydrochloric acid solution (x), which must be added to neutralize the total excess bicarbonate in the whole circulating blood is obtained approximately by the following formula: $x = 0.15 CW$, where C = the total carbon dioxid in percentage by volume over and above the normal (60 per cent. by volume), and W = the weight of the patient in pounds. The constant (0.15) was obtained on

the assumption that the total blood weight is 8 per cent. of the body weight, the specific gravity of the blood, 1.05 per cent. and the bicarbonate content of the blood 95 per cent. of the total carbon dioxid. It must be understood that the injection of hydrochloric acid intravenously cannot be recommended, as we have had insufficient experience with its use. It is suggested as a therapeutic agent from theoretical considerations. We have never seen any toxic effects in dogs. It should be combined with an equal amount of physiologic sodium chlorid solution, so that the final concentration of hydrochloric acid is one twentieth normal.

In order that the chemical findings may be more easily reviewed, the cases have been summarized and presented in the accompanying table.

In brief, the series consists of seven patients, five of whom had obstructions at the pylorus, two from ulcer and three from carcinoma. One patient had an annular carcinoma of the jejunum, and another suffered from persistent postoperative gastric dilatation, with vomiting. All of the patients had an increased plasma carbon dioxid capacity; all but one had hypochloremia, and all of those tested showed an elevation in blood urea. The three patients who showed the greatest change in bicarbonate content developed spasms. Before further discussion of these findings, it might be of interest to take up the results of a few experiments with dogs, performed recently.

RECENT EXPERIMENTAL WORK

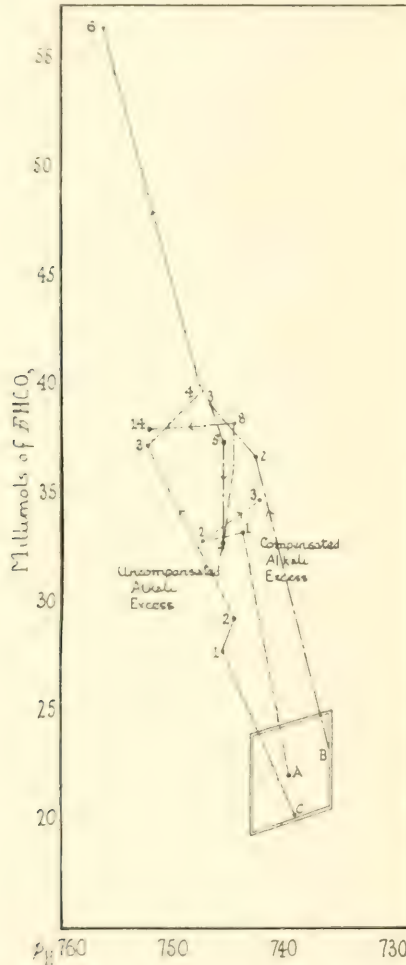
The pylorus was occluded in a number of dogs, and arterial and venous blood was examined at intervals before and after operation. In some dogs, a duodenal bucket-tube was introduced through the wall of the stomach, so that the contents of the stomach could be washed out regularly and the secretion analyzed. In three dogs, another tube was inserted into the duodenum below the obstruction, so that a high fluid intake could be assured.⁴⁷

It was found that after operation there was a rapid rise in the plasma bicarbonate, which in the dogs that developed tetany was not compensated for by an equivalent rise in free carbonic acid, so that a decrease in hydrogen-ion concentration resulted according to the accepted formula: $[H] = \frac{k [H_2CO_3]}{y [BHCO_3]}$. The hydron was measured by Cullen's new colorimetric method for plasma which dispenses with dialysis.⁴⁸ Precision in preparing the standard solutions, care in collecting unobstructed blood under oil and avoiding contact with air are

47. To Dr. W. E. Swift we are indebted for the suggestion of using these two procedures simultaneously. The method proved very satisfactory.

48. Cullen, G. E.: *J. Biol. Chem.* **52**:501, 1922.

essential, but otherwise the technic is short and presents no difficulties. The consistency of our results gave us confidence in their accuracy. In all the dogs in which there was a marked rise in p_H , tetany developed, and there was no dog with tetany whose p_H was not definitely increased. There was then, in the true sense of the word, an alkalosis. If the



Values for HCO_3 and p_H in the venous blood of three dogs who developed tetany after pyloric occlusion. The numbers refer to days after operation. The limits of normality as determined by blood analyses in seven dogs is indicated by the parallelogram.

series was not so small (seven), we might believe that an increased p_H was invariably present in gastric tetany. It might make clearer the effect of pyloric occlusion on the acid-base equilibrium if the results in

the three dogs that developed tetany, were presented graphically according to the chart constructed by Van Slyke⁴⁹ to show all possible changes in the acid-base balance. The figures for combined carbon dioxide (bicarbonate) are plotted as ordinates, the p_{H} as abscissas. The parallelogram in the center includes all values for normal dog's blood found in the seven experiments.

It will be seen that, very soon after the operation, a compensated, and later an uncompensated, state of alkalosis developed. This change was associated with a state of tetany.

Measuring the chlorid content of the gastric secretion, it was found that, in each twenty-four hour period, more than enough chlorid was secreted, and thus lost to the body, than was necessary to account for the decrease in the concentration of this ion in the plasma.

It was also discovered that the concentration of urea and nonprotein nitrogen in the dog's blood increased after operation. The rise commenced on the second or third day (i. e., later than the change in p_{H}), and apparently fluctuated independently of the other factors (p_{H} , bicarbonate and chlorid).

In taking electrocardiograms of two dogs, it was found by chance that in both cases the electrical resistance of the skin and tissues had increased more than threefold after operation. This is of interest in connection with the decreased serum conductivity found in Case 5.

COMMENT

It is clear that experimental results corroborate clinical findings. The loss of hydrochloric acid from the body is evidently the primary cause of the hemic disorder. In lower intestinal obstruction, there is a loss of alkaline juices as well as acid, so that, although the plasma chlorid decrement is marked, there is no alkalosis. For instance, in the reported case of a chronic jejunal obstruction, there was only a slight rise in carbon dioxide, whereas the fall in chlorids was considerable. When the obstruction occurs at the pylorus, however, hydrochloric acid, for the most part, is expelled. Essentially, this means a loss of hydrogen ions and chlorid ions from the blood. Withdrawal of the former frees acid radicles (mostly HCO_3^- ions) and of the latter, basic radicles (mostly Na^+ ions). The union of the freed ions (NaHCO_3) results in an increased value for total carbon dioxide, as obtained by the Van Slyke method in the cases described. The rise in plasma bicarbonate measured in mols, however, is not equivalent to the fall in chlorid, being usually only about one half as great. This fact is consistent with the finding that a large fraction of the chlorid in the stomach contents is not in the form of hydrochloric acid. The greater

49. Van Slyke, D. D.: J. Biol. Chem. **48**:153 (Sept.) 1921.

part of this excess chlorid is probably neutral salt derived from the saliva which has become mixed with gastric juice.

The rise in bicarbonate as explained above is evidently not compensated for by an equal rise in free carbon dioxid (carbonic acid); and the ratio carbonic acid : sodium bicarbonate is disturbed, with a result that the hydrogen-ion concentration is diminished (rise in p_H), and the blood is consequently more alkaline.

The significance of the increase in the nitrogen catabolites of the blood in pyloric occlusion is problematical. In intestinal obstruction, numerous observers⁵⁰ have found that all the nonprotein nitrogen fractions are high, but the reason for this is not certain. Chemical uremia has never been reported as an accompaniment of pyloric obstruction; but as it occurred to some degree in all our patients, and as it was also present in most of the dogs, it would seem that there was a definite association of the two. In neither dogs nor human beings was there any apparent relationship between the urea concentration and any of the other substances analyzed. The rise in urea, it seems, came on after the rise in total carbon dioxid, and in two of the human cases continued to increase after operation, despite the fact that the carbon dioxid returned to normal. As there is usually no ingestion of nitrogen in these cases, the rise in the blood has been taken to indicate either an increased protein catabolism in the tissues or a block in the portal of elimination.

Light might be thrown on the problem by comparative estimations of the blood urea and the amount excreted in the urine over a given period (MacLean index, etc.). From the fact that a rise in p_H has been found to accelerate metabolism in some lower forms of life, the hypothesis that alkalosis hastens protein catabolism in pyloric stenosis might suggest itself. This question cannot be answered at present. But in view of the fact that in our cases the ascent of urea continued for sometime after the total carbon dioxid had dropped to normal, the second theory, namely, that ingestion of alkali temporarily affects renal function, seems more acceptable. A mild nephritis has been thought to be present in intestinal obstruction since the experimental studies of McQuarrie and Whipple,⁵¹ who found that the nitrogen and chlorid excretion was impaired and the phenolsulphonephthalein elimination was subnormal. In the clinical cases recorded, we have no estimations of

50. Ellmore, Wilder and Comfort, C. W.: *Arch. Int. Med.* **14**:620 (Oct.) 1914. Cooke, J. V.; Rodenbaugh, F. H., and Whipple, G. H.: *J. Exper. Med.* **23**:717 (June) 1916. Lourin, H. W.: *Blood Urea Nitrogen in Acute Intestinal Obstruction*, *Arch. Int. Med.* **27**:620 (May) 1921.

51. McQuarrie, L., and Whipple, G. H.: *J. Exper. Med.* **29**:397, 421 (April) 1919.

nitrogen metabolism, such as the ratio urea in blood: urea in urine. In one case, the phenolsulphonephthalein output was low (20 per cent.).

There is some evidence that ingestion of alkalis will damage the kidneys. Large amounts of alkali by mouth have been found responsible for albumin in the urine. Albumin and casts were frequently found in our human as well as in our animal cases. This coincides with the experience of Mayo-Robson, who calls particular attention to this finding in gastric tetany. It is possible, therefore, that a rise in bicarbonate (or p_H) causes a temporary functional nephropathy, and that subsequently, as in nephritis, the concentration of the nitrogen waste products in the blood rises.

It was thought at first that, with a more alkaline blood, less ammonia would be formed and excreted in the urine, and that the nitrogen thereby released would increase the urea factor. The rise of the urea nitrogen and the nonprotein nitrogen proportionately, however, were too great to be accounted for simply by a diminution in ammonia production. Nevertheless, we would confidently expect to find the urea: ammonia ratio in the urine increased. As has already been mentioned, a number of observers have found that, after overventilation, the urinary ammonia decreased markedly, but unfortunately these tests have not been made in cases of gastric tetany.

It is to be regretted that a more complete study of the urine was not made in our cases. The usual routine observations record the fact that it was almost invariably acid to litmus despite the increased alkalinity of the blood. Two tests on the urine of dogs with alkalosis showed that it was acid to phenol red and alkaline to methyl red; i. e., the p_H was about 5.8 to 6.4. Palmer and Van Slyke⁵² noted in bicarbonate feeding experiments that, in disease, the urine did not become more alkaline than blood (p_H 7.4) until a higher plasma carbon dioxide had been reached than that of normal controls. In one diabetic, the carbon dioxide rose to 104.4 per cent. by volume before the urine became alkaline. This is difficult to explain, but is at least in agreement with our findings. Marshall⁵³ has recently found that it is practically impossible to raise the reaction of urine above p_H 8 by the ingestion of alkali.

Having settled on the important changes in the blood, namely, a rise in p_H , and total carbon dioxide, a fall in chlorids and an increased concentration of the nitrogenous waste products, it would be satisfactory to be able to explain a causative relationship between one or more of these factors and the state of tetany. Unfortunately, this cannot be done with certainty.

52. Palmer and Van Slyke: Footnote 21.

53. Marshall, E. K., Jr.: J. Biol. Chem. **51**:3 (March) 1922.

The possible effect of chemical uremia on irritability cannot be entirely disregarded. Because of its association with terminal coma, the accumulation of waste products in the blood has often been regarded as depressing to the nervous system. It is striking that in all our cases, human and animal, there was invariably an increased concentration of urea in the blood when tetany developed. Also a large number of the reported cases of tetany following bicarbonate therapy occurred in patients with damaged kidneys. In Harrop's case⁵⁴ the woman was suffering from mercuric chlorid poisoning and developed tetany, with carbon dioxid around 80 per cent. by volume. Morse⁵⁵ reported a case of long-standing pyelitis in a child with a high blood urea who developed tetany after sodium bicarbonate therapy, even though the plasma carbon dioxid was constantly below normal.

As our results add nothing beyond what has already been proved experimentally bearing on the possible relationship between tetany and the anion or cation balance, no contribution can be made to this aspect of the question. Our clinical and experimental data direct attention to the acid-base disturbance as the primary causative factor in gastric tetany. Fundamental experiments have shown that the addition of alkali heightens irritability,⁵⁶ possibly by increasing the permeability of the nerve sheath;⁵⁷ the injection of basic carbonates and phosphates cause tetany, and in two clinical forms of tetany (that which follows overbreathing, and so-called gastric tetany), an increased p_H is found. With this evidence, it seems reasonable to conclude that preponderance of base may cause nerve hyperirritability. Whether this action is direct or indirect, i. e., acting through an influence exerted upon the sodium:calcium ratio, has not been certainly proved.

It has been pointed out that inferences based upon the work of Freudenberg and György to the effect that the shift in basic radicles from ionized salt compounds to less dissociated protein molecules, with rise in p_H , involves mostly the calcium ions, and consequently the sodium:calcium ratio in the plasma is increased, are probably erroneous. Explanations for the effect of p_H on the sodium:calcium ratio which involve peculiar properties of the calcium ion seem more likely, but cannot be appropriately discussed at present.

DIAGNOSIS AND TREATMENT

With a patient who gives a history of persistent vomiting, particularly in large amounts, it is well to determine the plasma carbon

54. Harrop, G. A., Jr.: Footnote 22, *loc. cit.*

55. Morse, J. L.: New York M. J. **112**:965 (Dec. 18) 1920.

56. McClendon, J. F.: J. Biol. Chem. **28**:135 (Dec.) 1916.

57. Osterhout, W. J. V.: Science **45**:97, 1917.

dioxid content or capacity. If it is much increased, i. e., over 80 per cent. by volume, without a history of alkali therapy, it is an indication that there is an obstruction, organic or functional, near the region of the pylorus and that the physicochemical balance of the blood is in jeopardy. If the carbon dioxid continues to rise, tetany can be predicted (in all our cases, the carbon dioxid was over 100 per cent. by volume before tetany ensued). But when sodium bicarbonate is rapidly injected intravenously, tetany may develop when the carbon dioxid is between 80 and 90 per cent. by volume; and at that point, death will be imminent unless relief measures are instituted. Mayo-Robson once wrote that "it has almost been made a criterion of the disease that it should end fatally."

In a case of tetany, a differential diagnosis must be made, especially between: 1. Hypoparathyroidism, which includes infantile tetany (often associated with rickets) and postoperative tetany (the occasional sequel of a thyroidectomy). This type is characterized by a low calcium content of the blood, and also, we are informed, by the presence of methyl guanidin in the blood and urine. 2. Tetany of hyperpnea, a condition which is marked by a high p_H but a low carbon dioxid content. This type, which seems frequently to be a manifestation of hysteria, has been clearly defined by Goldman,⁵⁸ and should be kept in mind in nervous patients. 3. Gastric tetany, which follows occlusion, at or near the pylorus and is characterized by a high p_H , a high carbon dioxid, a low chlorid and probably a high urea concentration. 4. Tetany following the intake of alkalis or sodium salts. In this instance, the diagnosis is made on the history. The blood, depending on the salt used, may show a high p_H and carbon dioxid content and a low calcium content.⁵⁹ In other words, a diagnosis can be made on purely chemical evidence. In fact, some cases can be diagnosed only on this basis. In one case reported from the Presbyterian Hospital,⁶⁰ the patient developed tetany in the course of an attack of sprue. It was found that the carbon dioxid content was normal, but the calcium content was definitely subnormal. Another case of sprue that had tetany as a complication had both an alkalosis and a low calcium content. At present, such forms can be classified chemically only. It is singular to us that tetany does not develop more frequently in cases of hypertrophic pyloric stenosis of children. Reports of two cases were found, but in both instances, soda had been used in the feedings.⁶¹

58. Goldman, Alfred: *Clinical Tetany* (J. D. Lippincott Co., Philadelphia, Pa.), M. A. **78**:1193 (April 22) 1922.

59. Tisdall, F. F.: Footnote 11. Binger, C.: Footnote 19, second reference.

60. Barach, A. L., and Murray, H. A., Jr.: Tetany in a Case of Sprue, J. A. M. A. **74**:786 (March 20) 1920.

61. Townsend, C. W.: Boston M. & S. J. **150**:154, 1904. Rice, C. V.: J. Oklahoma M. A. **14**:238 (Sept.) 1921.

For a complete diagnosis, then, the p_{H} and carbon dioxide content of the unobstructed venous (or preferably the arterial) plasma, and the chlorid and the calcium concentrations should be estimated. The blood urea is of interest. These findings suggest that the existing textbook classifications of tetany, which are based for the most part on its association with other clinical conditions, are confusing and might with benefit be revised.

The treatment of gastric tetany is operative, except in cases of pyloric spasm (which might theoretically cause tetany, but of which no proven case has been found in the literature). The indication for operation, of course, is the obstruction, which must be relieved; and the method chosen should be adapted to the pathology in the given case, i. e., gastro-enterostomy, pyloroplasty, pylorotomy, etc. As a supporting measure, administration of fluids is essential. Patients are frequently dehydrated, as little water passes through the pylorus in severe cases, and the absorption from the gastric mucosa is minimal. Granting that the loss of hydrochloric acid is the cause of the condition, rational therapy would seem to consist in the replacement of this acid, preferably by intravenous injections. Large amounts of acid can be given to dogs with safety; and 500 c.c. of tenth-normal hydrochloric acid solution plus 500 c.c. of 0.15 normal sodium chlorid solution was administered to one of our patients without deleterious effects. Although from this evidence we are inclined to think that a dilute solution of acid in saline solution can be injected with benefit, our experience has been too limited to create assurance. MacCallum states that infusions of normal saline were efficacious. The addition of a 0.5 per cent. solution of calcium chlorid would theoretically be of advantage, but the hemolysing power of these solutions will have to be tested before their administration is adopted as a therapeutic procedure. The amount of hydrochloric acid necessary to neutralize the excess bicarbonate can be roughly estimated as outlined in the discussion of Case 7. Calcium chlorid must not be injected subcutaneously, since it is irritating to the tissues.

CONCLUSIONS

1. Five cases of pyloric stenosis are reviewed. Two other cases with somewhat comparable findings are included; one patient had post-operative gastric dilatation; the other, carcinoma of the jejunum with stenosis.
2. With stenosis of the pylorus, hydrochloric acid cannot pass into the intestines and be reabsorbed. It is expelled by vomiting or washed out by gastric lavage. The result is a disturbance of the acid-base balance in the blood and tissues.
3. The blood findings in our patients were similar to those in dogs after experimental pyloric occlusion, namely, an increased carbon dioxide

and urea and a diminished chlorid content. The most abnormal values found were: carbon dioxid, 107 per cent. by volume; chlorid, 2.5 gm. per liter, and urea 334 mg. per hundred cubic centimeters.

4. In the dog experiments, it was found that the blood was more alkaline than normal.

5. There is almost certainly a relationship between the recorded blood changes and the condition of tetany that may develop in severe cases.

6. It is considered that the cases presented, the experiments summarized and the literature cited make the assumption that nerve irritability is increased by a fall in the hydrion concentration of the blood or by a rise in the sodium:calcium ratio highly probable. The latter may be brought about by adding dissociable sodium compounds or precipitating calcium. Whether the hydrogen ion is active because of its effect on the cation ratio is still an open question.

7. The increased electrical resistance found in two dogs and the lowered serum conductivity in one patient are very suggestive and needs investigation.

8. The treatment of gastric tetany is operative. As far as we know, it is always the result of obstruction of the pylorus, due to gross pathologic changes. There are other forms of tetany that are not associated with pathologic gastric conditions, from which it must be differentiated. This can usually be done by suitable blood analyses.

CONCLUSION

Pyloric stenosis, particularly when attended by persistent vomiting, is followed by a rise in the total carbon dioxid and a fall in the chlorid content of the blood plasma, and later, it seems, by an increase in the nitrogen catabolites.

There appears to be a causative relationship between these findings and nerve hyperirritability.

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Am. Med. Assoc., June 17, 1920.*
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28 1923
EXPERIMENTS WITH HODGKIN'S DISEASE
AN ATTEMPT TO PRODUCE IT IN ANTHROPIDS AND
OTHER MONKEYS

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These experiments were made in an attempt to produce Hodgkin's disease in chimpanzees and rhesus monkeys. The apes were chosen because numerous attempts were made to produce this disease in lower animals. Feeding experiments and injections of gland extracts have been made on guinea-pigs, rabbits, ring tail and rhesus monkeys.¹ Certain hyperplasias have been produced, but it has been shown that the injection into animals of normal gland extracts causes a lymphatic hyperplasia.

For a working basis the following premises were adopted: 1. Hodgkin's disease is a distinct clinicopathologic entity. 2. It belongs to the group of infectious granulomas and is of bacterial or protozoan origin.

The results obtained were all negative, but it is believed that they should be recorded because the biologic similarity between chimpanzees and man make the findings of more significance in regard to the transmissibility of the disease by implantation of tissue.

ANIMALS

Before procuring the chimpanzees, it was necessary to learn something of the habits and living conditions of these animals, and many months were spent in veterinary consultations and going over plans for proper housing and caging. After securing the animals, the next step was to determine, as far as possible, that they were free from disease. Such conditions as eczema, pyorrhea alveolaris and round worms, were very troublesome. Wassermann tests were made and also complement-fixation tests for tuberculosis. The latter were felt to be important, owing to the susceptibility of apes to this disease. The two chimpanzees gave positive reactions, but they showed no evidence of tuberculosis while under our observation from Oct. 28, 1906, until May, 1920.

* This work was carried on under a grant from the Rockefeller Research Fund.

* From the laboratories of the department of anatomy, Columbia University.
1. Reed: Bull. Johns Hopkins Hosp. No. 10, 1906, p. 155. A. Sargant, Bulletin Aver Clinical Lab. No. 4, 1907. Epstein, C. H. and Yates, J. G.: An Etiologic Study of Hodgkin's Disease, J. A. M. A. **61**:1803 (Nov. 15) 1913; An Etiologic Study of Hodgkin's Disease, **62**:516 (Feb. 14) 1914. Schaeffer, E.: Berl. klin. Wchnschr. **51**:1215, 1914.

Apparently, tuberculosis runs its almost uniformly fatal course in these animals within eighteen months under the zoologic and circus conditions of New York City.

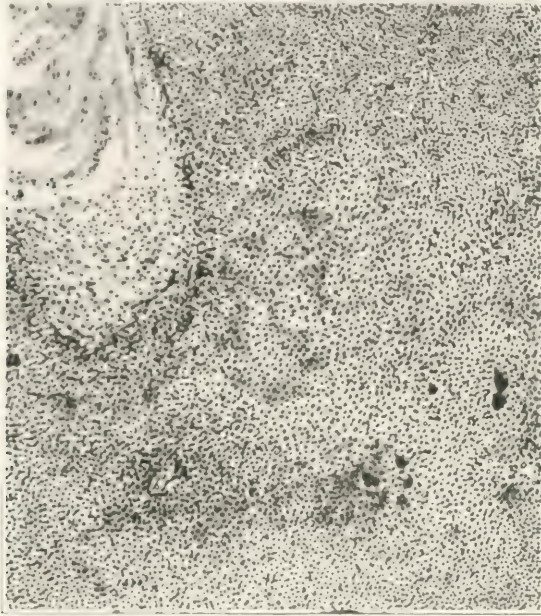


Fig. 1—Low power reproduction of drawing of gland used in Experiment 1.

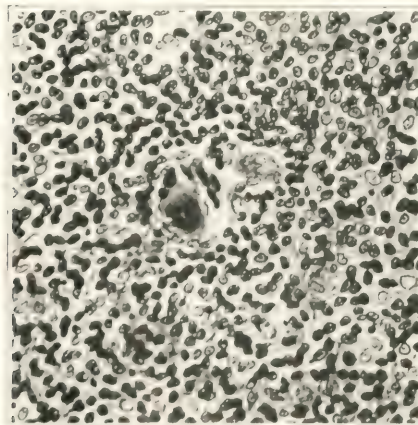


Fig. 2—High power reproduction of drawing of gland used in Experiment 2.

Both chimpanzees were immature females. They were in the process of shedding their baby teeth and were judged by an expert from the Bronx Zoological Park to be about 4 years of age.

EXPERIMENTAL WORK

Experiment 1.—A group of three nodes was removed from a man, 23 years of age, who first noticed an enlargement in the neck eight months previously. Later lymphomas developed in the axillae. These showed the typical histologic picture of Hodgkin's disease (Fig. 1).

A slice of a node 1.5 by 0.3 cm. was transplanted into the retroperitoneal region and one 0.7 by 0.5 into the spleen of a rhesus. The animal was observed for five months, and no external evidence of Hodgkin's disease was noted.

The rhesus was then used for a poliomyelitis experiment and died. Necropsy was performed and microscopic examinations were made, but no evidence of Hodgkin's disease was found.

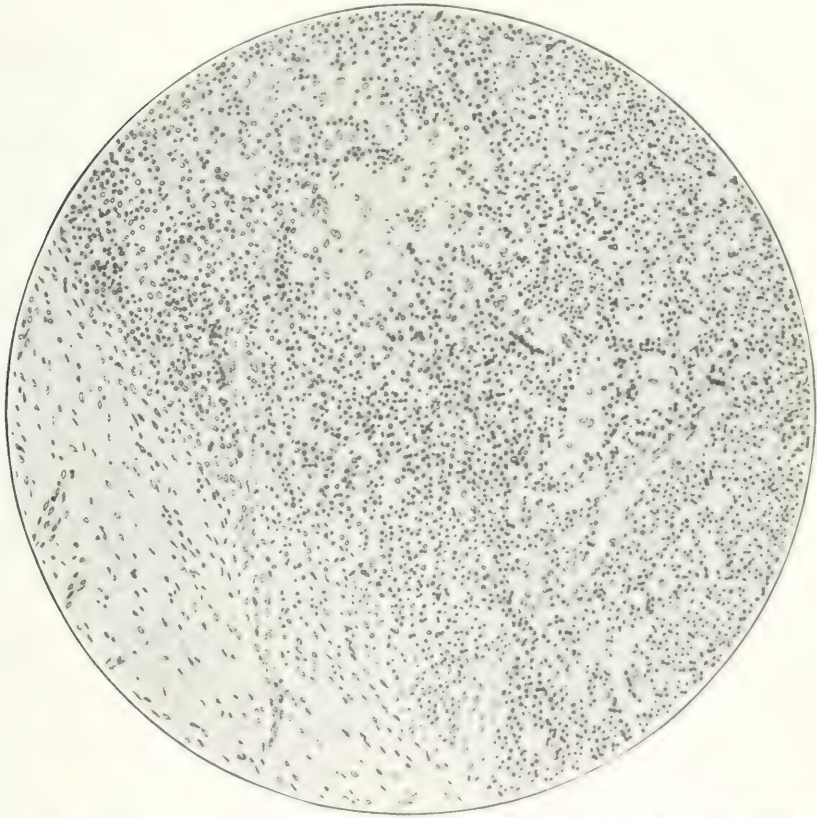


Fig. 3.—Low power reproduction of drawing of gland used in Experiment 2.

Experiment 2. Glands were removed at the Roosevelt Hospital from the groins of a man, 30 years of age, who had been suffering from weakness, night sweats and lymphomas in the axillae, neck and groins.

Histologically the glands were those of Hodgkin's diseases (Fig. 2).

Bacteriologic examinations were made of the glands, but no organisms were isolated.

Two pieces of nodes, 1.5 by 0.4 cm. and 1 by 0.4 by 0.3 cm. were transplanted into the retroperitoneal region and spleen of a young rhesus. The animal was used for a poliomyelitis experiment, and died of abscess of the brain. At

nevertheless no evidence of Hodgkin's disease was found. Histologic examination showed scar tissue in the spleen at the site of transplantation.

Experiment 3.—Glands were removed from a man, about 37 years of age. This patient showed the first signs of Hodgkin's disease two years previously, and the nodes were removed at that time to confirm the diagnosis.

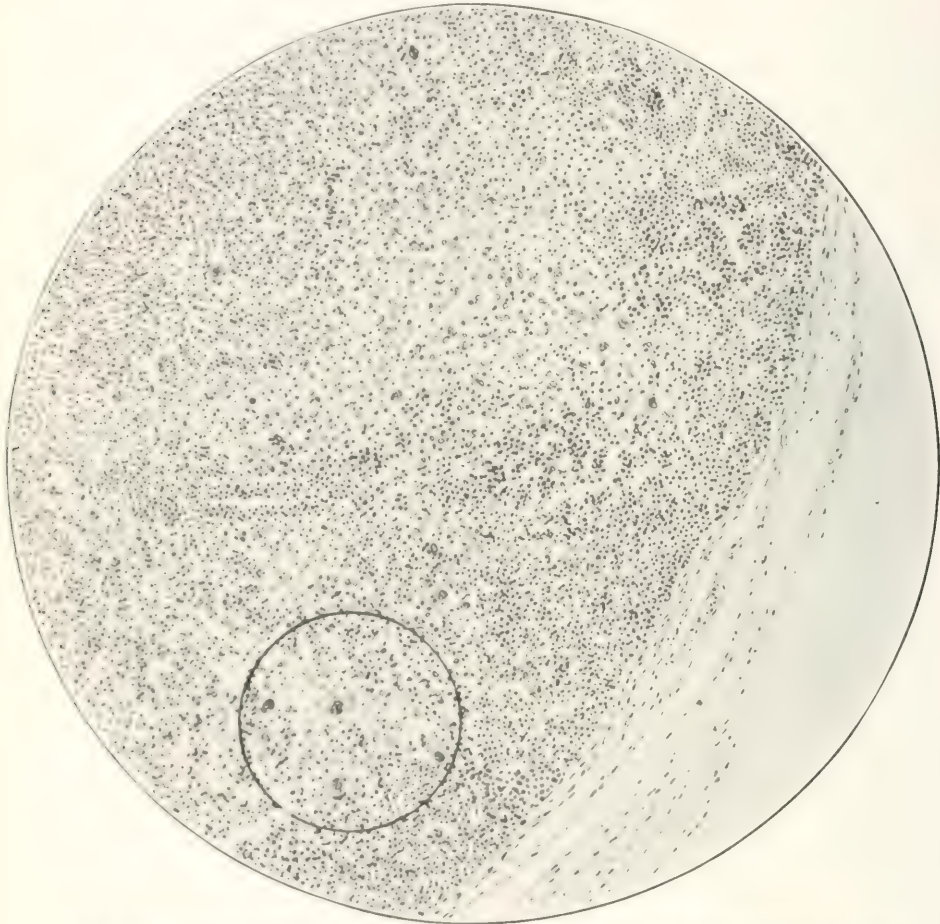


FIG. 4.—Low power reproduction of drawing of gland in Experiment 4. The part within the circle is represented in Figure 5.

In June, 1919, a gland was removed from the inguinal region, and a section 2 by 1 to 4 cm. was transplanted beneath the deep cervical fascia of a female chimpanzee about 6 years old.

Sections made from the gland (Fig. 3) were typical of Hodgkin's disease. Cultures made at the time of transplantation revealed diphtheroid bacilli in Petroff's culture medium and broth, and staphylococci in broth. The wound healed without infection. The animal died in November, 1919.

Experiment 4.—Glands were removed from a boy, aged 15 years, who gave a two years' history of swellings in the right side of the neck and right axilla.

In July, 1919, glands were removed from the cervical region and a slice of gland 3 by 2 by 1 cm. transplanted under the deep cervical fascia of a female chimpanzee about 6 years old.

The histologic picture was that of Hodgkin's disease (Figs. 4 and 5).

Anaerobic and aerobic cultures made from the gland at the time of transplantation revealed *Staphylococcus albus*, but the wound healed without infection. The animal was in perfect health two years after the experiment.

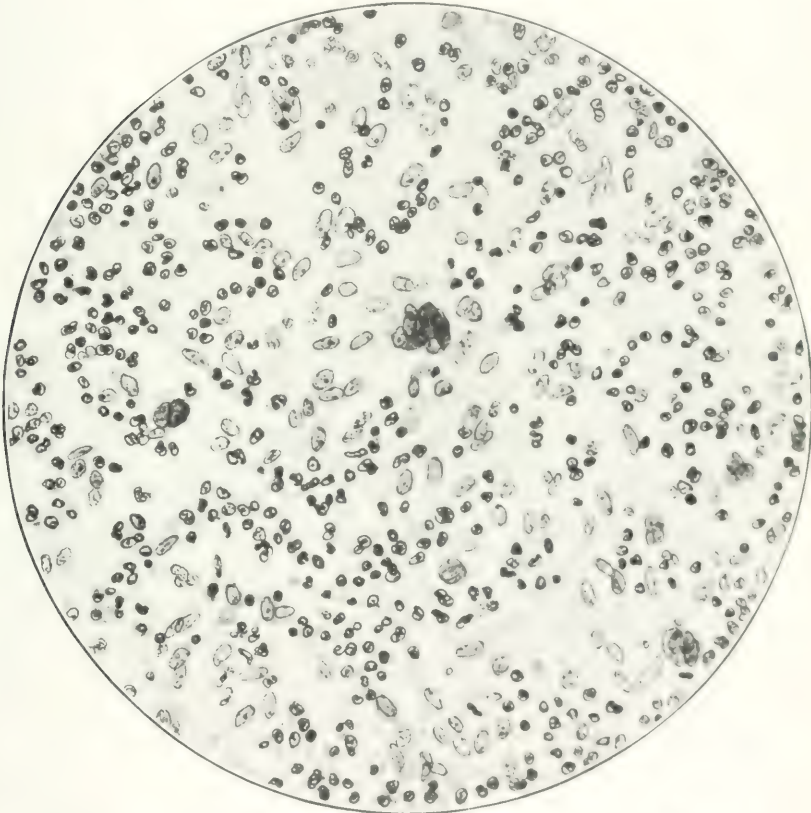


Fig. 5.—High power reproduction of field within circle in Figure 4

COMMENT

The two rhesus monkeys were observed five and six months, respectively, and at necropsy showed no evidence of lymphomas.

The two chimpanzees were observed for about two years in our cages after the transplants were made and showed no external evidence of Hodgkin's disease. They were then used as exhibition animals in a circus. The one used in Experiment 3 died in November, 1921, the diagnosis by the veterinary surgeon being tuberculosis. Necropsy was not performed.

The second chimpanzee was taken ill about this time, the prominent symptoms being cough, loss of weight and fever. She died Feb. 5, 1922. Necropsy was performed forty-eight hours postmortem, the anatomic diagnosis being: Tuberculosis and edema of the lungs; tuberculosis of the cervical, tracheal and mesenteric lymph nodes; tuberculosis of the spleen, miliary and caseous; tuberculosis (?) of solitary follicles of the ileum; tuberculosis, miliary, of the liver. Microscopic examination was made of the lungs, lymph nodes, liver, spleen and intestines. The lungs presented an advanced degree of caseation, with the formation of tubercles without giant cells. The lymph nodes and spleen presented a similar picture. The liver presented marked fatty infiltration with pronounced postmortem change and a few small areas of necrosis, the nature of which was not determined. The kidneys also presented postmortem change, but no evidence of tuberculosis. On the mucosal surface of the ileum was a small ulceration with fibrosis and round cell infiltration.

Tuberculosis in chimpanzees is a rapidly fatal disease and there is little doubt that the infection took place after the animals left our cages. We have found no evidence that Hodgkin's disease has been produced in the rhesus monkeys and chimpanzees used in these experiments.

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THE CRANIAL SUBDURAL SPACE (A METHOD OF STUDY)

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Pathological accumulation of fluid in large quantity between the dura mater and arachnoidea was described in an earlier communication.¹ This fluid was found to have a higher specific gravity and higher concentration of protein than the cerebrospinal fluid, the two fluids being obtained simultaneously. The concentration of easily diffusible substances such as glucose was identical in the two specimens, while their cellular content was always different. During this time drainage of the cerebrospinal fluid continued normally in the subarachnoid spaces beneath the subdural collection.

Interest in the condition described above led to study of the relation between the dura and arachnoidea in animals. An attempt was made to induce a fluid exudate beneath the dura by various inflammatory and infectious agents placed on the outer surface of the dura. Details of these experiments will be omitted, as little if any increase was caused in the subdural fluid. The following description applies to the normal animals used as controls.

Is the space between dura and arachnoid a truly potential space or does it normally contain fluid? To answer this question an attempt was made to aspirate fluid with fine needles and likewise to inject dye beneath the dura. It was impossible to exclude the presence of cerebrospinal fluid as the result of injury to the pia-arachnoid by this method. Consequently, the technique described below was used.

¹Penfield, W. G. Subdural effusion and internal hydrocephalus. *Am. Journ. Diseases Children*, vol. 26, pp. 383-390, 1923.

A 10 per cent solution of formalin containing a physiological concentration of sodium chloride was injected into the internal carotid of an anesthetized dog. A pressure sufficient to overcome the blood pressure in this artery was used, i.e., about 200 cm. The animal was taken at once to the refrigerator and frozen at a temperature a little below 0°C. At the end of five to fifteen days the head was sawed into slices by parallel cuts. By gentle pressure, the segment of brain included in a slab could then be pushed out. The pia-arachnoid, frozen in its layer of cerebrospinal fluid, was carried out with the brain segment. A layer of clear yellow ice was then found on the under surface of the dura or loosely applied to the outer surface of the arachnoid.² The cut surface of the brain presents minute cavities.

This amber-colored sheet of ice is thus found over the convexity of both cerebral hemispheres. It is entirely free. Its outer surface, corresponding to the dura, is smooth and glistening. Its under surface, which is in relation with the arachnoidea, is not so smooth, but minutely pitted. This ice sheet was often found to be 0.5 to 1 mm. in thickness over the convexity of the cerebrum, but usually thin beneath the falx. Considerable variation in the amount of subdural fluid exists, even in normal dogs. If the ice crystals be picked up and placed in a bottle, the resultant fluid varies from a drop or two to 1 cc. in dogs of 5 kilograms.

It is difficult to demonstrate the subdural ice over the cerebellar arachnoid in some animals, but in others beautiful clear crystals can be lifted with the forceps from the under surface of the tentorium. No similar layer of fluid was demonstrated beneath the spinal dura over the cervical cord.

The appearance of the frozen layer of fluid in the pia-arachnoid is different from the above. It is colorless. Incorporated in it are the trabeculae of the pia-arachnoid, and

² When the animal is frozen without preliminary formalin injection, as was done by Austmann and Moorhouse, it is not possible to push out the brain slabs in this way nor to obtain a line of cleavage on the outer surface of the arachnoidea. Austmann, K., and Moorhouse, V. On the function of the cerebral ventricles. *Am. Journ. Physiol.*, vol. 66, pp. 267-274, 1923.

even from the cisterna cerebello-medullaris the ice cake can only be removed by tearing it free from its membranes. The difference in color indicates that the subdural fluid does not take part in the cerebrospinal fluid circulation.

Finally, the cerebral and cerebellar subdural space is more than a potential cavity in normal dogs. It contains a variable amount of clear yellow fluid which is distinct from the cerebrospinal fluid.

204 (2436)

Visualization of the gall bladder of the dog by the Roentgen ray.

By HAROLD A. ABRAMSON.*

[From the Laboratories of the Department of Surgery, Columbia University, New York City.]

By injecting solutions of sodium iodide or Neo-silvol (Parke-Davis) into the gall bladder of the dog, the movements of the gall bladder and the fate of contained fluids may be easily studied fluoroscopically and by radiograph. Neo-silvol, a silver-protein-iodide compound, is particularly useful because it is not readily absorbed and is relatively non-irritating. Excellent radiographs of the gall bladder have been obtained after direct injection of 1 cc. of a 35 per cent solution of sodium iodide. The volume of the gall bladder in a medium sized dog is greater than $2\frac{1}{2}$ cc. Much more of the salt may therefore be used, and isotonicity still be preserved since sodium iodide is isotonic at about a concentration of $14\frac{1}{2}$ per cent. Proportionate amounts of Neo-silvol may similarly be used. The presence of pneumoperitoneum remaining postoperatively or induced experimentally, is a distinct aid in visualization where it is desirable to use small concentrations of material.

The following observations have been made on six dogs while recovering from anesthesia, after anesthesia, or a number of days after operation. The total number of actual experimental hours of observation was between fifteen and twenty.

*Introduced by Reuben Ottenberg.

1. *Spontaneous Expulsion.*

Only once during the course of this series was there seen spontaneous expulsion of material from the gall bladder. This was in a cholecystostomized dog (No. 3361, May 29, 1923) which five days after a small bored rubber tube had been placed in the gall bladder wall, was taken to fluoroscopy. Four cc. of 150 per cent sodium iodide was injected through the tube. The gall bladder became beautifully outlined. During the next ten minutes the dog was standing comfortably on the platform on four legs, or occasionally sitting down, nothing was seen to enter the duct and go into the duodenum. After that period the material inside the gall bladder was then seen to distend the cystic and common duct, and several globules of sodium iodide left the common duct and passed into the duodenum, moving slowly, propelled by peristalsis of the gut. The ducts then disappeared from view. For the next half hour nothing more left the gall bladder. Since actually observed material, estimated at 3 cc., left the gall bladder, the gall bladder contracted, actively or passively, expelling the mentioned volume. It must be remembered, however, that this was observed five days after cholecystostomy had been performed, and there was a tube still through the wall of the gall bladder.

2. *Pressure on the abdominal wall.*

In both intact and cholecystostomized gall bladders very slight pressure on the abdominal wall, laterally or antero-posteriorly, did not force sufficient material into the duodenum to make visualization possible. With increasing pressure, increasing amounts of the contained solution could be forced until very little remained and the collapsed, flaccid gall bladder was distinctly seen.

3. *Movements of the animal.*

Sitting up, lying down, or moving about by the dog, never resulted in the expulsion of the material in gall bladder in sufficient quantity to be seen by the fluoroscope.

4. *Respiration.*

At no time could respiration be said to cause enough material to leave the gall bladder to show fluoroscopically in the duodenum. While it may be said that very minute amounts might

have been forced out and not visualized, it is justifiable to state that if any had come through, in all probability it would have accumulated at some point at some time and would have been seen. At every fluoroscopic examination the patency of the ducts was tested with pressure on the abdominal wall. However, this much must be said in favor of the view that the change in intra-abdominal pressure produced by respiration forces material from the gall bladder. During respiration and with each inspiration there was a slight flattening along the longitudinal axis of the gall bladder. Hence with an organ whose internal pressure is greater than that in the duodenum, with a relaxed sphincter of Odi, it is conceivable that the change in shape might produce an overflow of contained fluid. It is important to think of the physics of the biliary tract as well as its physiology. The gall bladder is a markedly distensible bag, connected to the biliary system by a tube, the cystic duct, to the common duct and the hepatic ducts. At any moment there is a definite "cholestatic" pressure in these ducts and the gall bladder. The pressure in the duodenum may be considered almost proportional to that produced at the sphincter of Odi. Excluding spasms of smooth muscle and obstructive mechanical factors, it is simply obeying fundamental hydrostatic principles to state that when the pressure in the gall bladder is greater than that in the duodenum under the conditions mentioned above, bile will flow from the gall bladder into the duodenum, regardless of contractile power.

The method of study which has been just outlined was developed during an attempt to study the Meltzer-Lyons test fluoroscopically so that the effect of substances on the Ampulla of Vater could be seen directly by observations of material in the gall bladder. These studies are not yet ready to be reported. Quantitative expulsion experiments of Neo-silvol from the gall bladder over a given period of time are also incomplete, as well as the contractility of the gall bladder under increasing intra-gall bladder pressure.

CLINICAL DEDUCTIONS FOLLOWING A STUDY OF BONE REPAIR.*†

By FREDERIC W. BANCROFT, M.D., F.A.C.S.,

NEW YORK CITY.

EVERY day sees the advance in importance of "Industrial Surgery." Economic loss through incompetence or carelessness in the treatment of fractures is more and more evident. So often we practice what I heard a surgeon lately remark in a discussion of a fracture, "When I have nothing to do, I put it up; when I have something to do, I put it off." "Studies of Bone Repair" may help us to understand many of the processes involved, and we should from this knowledge base a more rational method of treatment. Experimental work in medicine is of little importance unless it has some direct, practical application in our therapy of disease.

Before attempting to state what we know of bone repair, it is advisable to admit how little we as yet understand. Our knowledge has really only skimmed the surface.

We do not know, for instance, by what processes the architecture of cancellous bone is altered in certain orthopedic conditions. I recently saw a hip ankylosed in adduction; the x-ray pictures revealed an entire change of the arrangement of the cancellous bone. How did this change occur? If a tooth be removed, there is a change in the jaw. The prepared skeleton we have seen in dissecting rooms would not be our conception of living bones. Bone is a living tissue, that is subject to stresses and strains and to which it progressively undergoes adaptation.

Moreover, adventitious bone occurs in tissues not intimately a part of the skeleton. We find it in lymph nodes, arteries, ovaries, in fact in almost any connective tissue structure of the body, and we are at a loss to explain its occurrence.

Experimentally, bone has been produced in animals by ligating the vessels of the kidney. Microscopic sections of this kidney from one

to two months later show areas of true bone and calcification occurring in the parenchyma. Neuhoff, working in the laboratory of Surgical Research at The College of Physicians and Surgeons, New York, found bone almost universally in fascia lata transplants that he had made to fill a defect in the bladder.

As extraskeletal bone has the same microscopic and chemical characteristics of skeletal bone, we must produce a theory of bone formation, broad enough in its scope to include embryonic bone formation; repair of bone following injury and infection, and adventitious bone.

A study of embryonic bone formation and of adult bone shows that it is a connective tissue structure with the essential characteristic that it has its extracellular structure impregnated with calcium salts. Let us now see what occurs when a bone is broken and attempt to draw deductions from our observations of the process of repair.

1. *Description of gross changes in a fracture.*—Fractures of long bones are caused either by direct or indirect violence. A fracture by direct violence has such a force exerted that muscles, nerves and vessels must likewise be traumatized. A fracture due to indirect violence must similarly injure the soft tissues by means of the fractured ends of the bone. We, therefore, consider a fracture not only a broken bone but an association of injuries to muscles, vessels and nerves, and, in the region of a joint, possibly joint injuries. The immediate post-traumatic reaction must be intense. Hemorrhage occurs throughout muscle bundles and tends to follow fascial planes. The ecchymosis so frequently seen is often due to hemorrhage seeping through various planes and extending to the skin. Between the fractured ends there is extensive hemorrhage. If the periosteum is not torn, this may be limited by it, but in fractures wherein displacement occurs, the periosteum is usually torn and extensive hemorrhage extends from the bone ends. Edema, a

* Read at the Annual Meeting of the Medical Society of the State of New York, at Rochester, April 22, 1924.

† From the Laboratories of the Department of Surgery, Columbia University, College of Physicians and Surgeons.

natural sequence of local chemical irritation as in hemorrhage and laceration of lymphatics then also occurs. Clinically, we often see the tremendous swelling of a limb a short time after injury. If a fracture is explored four or five days after injury there is a beginning organization of the blood clot. At about ten days one finds a thick gluey-like material—the early callus—which joins the bone ends and injects adjacent muscle bundles. This callus has a peculiar consistency. If a rabbit's bone is broken and not treated so that the ends overlap, we have found on cutting down on the bone at the end of seven days and excising the surrounding muscles that the ends can be freely moved in a lateral direction, but it is almost impossible to draw these ends so that the overriding is obliterated. We have here then only the factors of the gluey callus because the muscles have been excised and muscle spasm has been eradicated. This experiment shows us why so often it is impossible with the patient under an anesthetic to reduce the existing deformity. A steady traction exerted over a considerable period of time will overcome this.

If, in the above experiment, this callus is cut into and scraped with a knife one feels distinctly gritty particles. This is the beginning ossification of the connective tissue. In about a month one finds on exposing the fracture that the signs of hemorrhage into the muscles have largely disappeared. The exuberant callus has been absorbed and around the fracture ends one finds an ovoid firm mass which cuts with difficulty, and in favorable cases, only slight motion can be detected between fracture ends. As repair progresses, the callus assumes more the natural shape of the bones and union occurs.

2. *Microscopic changes in fracture.*—Immediately following fracture, blood clot is seen between the fractured ends. At about five days there has been contraction of the fibrin and early granulation tissue is seen growing in from the periphery of the clot. Even at this stage one can see areas of denser staining in certain areas of the granulation tissue which is apparently beginning deposition of calcium salts on the intercellular stroma. At about ten days, connective tissue is well organized and there are numerous new blood vessels. In the perivascular areas one can see very definite osteoid tissue. At this stage there is quite a definite arrangement of blood vessels, areolar tissue and osteoid tissue. The arrangement is somewhat like the lobules of the liver; one finds blood vessels, surrounding them, an area of areolar tissue and at the periphery of this, osteoid tissue. No specific cell can be identified. There is a gradual transition in the appearance of the cells from connective tissue to osteoid tissue to bone. Figs. 4 and 6.



FIG. 4. Seventeen day callous following fracture. Shows deposition of calcium salts on the avascular zones in early connective tissue.



FIG. 6. High power view of Fig. 5. A—End of fractured shaft showing atrophy at end with absence of bone nuclei. B—New bone formation in the connective tissue. C—Areolar connective tissue with new formed blood vessels.

Where the periosteum has been torn the arrangement of osteoid tissue can be seen extending out into the muscles. Occasionally one sees areas of hyalin or fibro cartilage. Exactly what is the significance of the cartilage is difficult to state. The theory has been advanced that where there is false motion, cartilage forms in the early process of repair. Here one finds transitions of connective tissue to cartilage cells and bone cells. At the periphery of the mass it is difficult to tell where connective tissue cell ends and cartilage cells begin, or where cartilage cells end and bone cells begin. Figs. 1, 2 and 3.

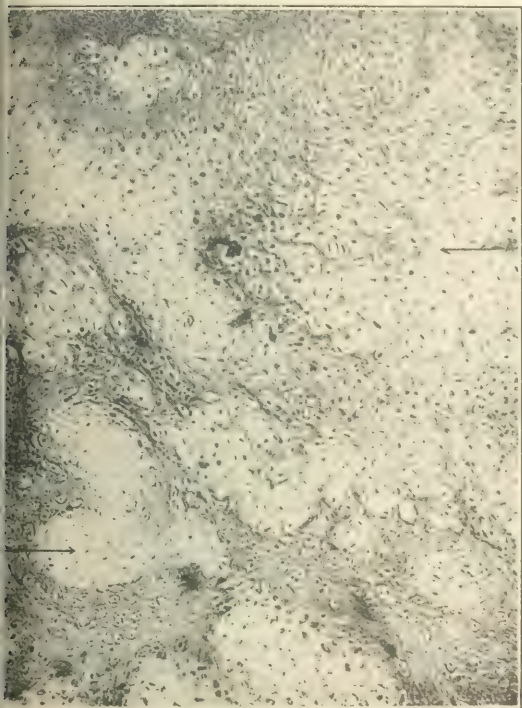


FIG 1. Early bone formation following fracture. A—Cartilage. B—New bone. C—Connective tissue. Gradual transitions are observed from connective tissue to cartilage, from connective tissue to bone, and from cartilage to bone. No distinctive cell seen.

Marked changes are noted in the ends of the fractured bones. The nuclei are absent in many of the bone lacunae and there are numerous large spaces in the ends of the bone which are apparently due to absorption of both matrix and cells. This atrophy of the bone ends is quite a noticeable factor, and one that has not been sufficiently emphasized. Sections taken at later periods show the lobula arrangement described in early callus but the osteoid is increased at the expense of the areolar tissue. This continues until a definite Haversian canal system appears. Calcium is apparently re-absorbed from the excessive exuberant callus seen in the early sections and scar tissue results.



FIG. 2. Curettings removed from fracture of humerus in human twelve days after injury. A—Fibro-cartilage. B—Early bone. C—Connective tissue.



FIG. 3. Ossification occurring in the midst of muscle fibers twelve days following a fracture of the humerus in an adult. A—Ossification occurring in cartilage. B—Early bone. C—Connective tissue. D—Degenerating muscle fibers.

Sections taken several months after injury show the re-establishment of the medullary canal and definite cortical bone, which is, however, of less density and contains more spaces for connective tissue than the normal cortical bone. Fig. 5.



FIG. 5. Comminuted fracture of radius and ulna in rabbit fourteen days after injury. A—Interosseus membrane. B—Medullary canal of radius with cortex on either side. C—New bone forming in connecting tissue following hemorrhage around the fractured ends and across the medullary canal. D—Detached bone fragments surrounded by new bone formation. E—Medullary canal of ulna.

The tendency of the Haversian canals at the zone of the fracture is to run at right angles to the cortex rather than parallel to it as in the normal. This is presumably due to the fact that the new blood vessels growing into the original granulation tissue were derived from the surrounding soft tissues and grew in this direction. The re-alignment of the vessels of the cortex probably does not take place until after a year. Where areas of periosteum have been stripped, a fibrous tissue membrane surrounds the bone, but it differs from the normal periosteum in that it has not the areolar tissue in the immediate proximity of the cortex.

In cases where there has been marked comminution of the bone, it is a well known clinical observation that there is a much greater output of callus than in a linear fracture.

3. *Physico-chemical theories of bone repair.*—Howland and Kramer found that the serum in tissue fluids of normal infants contain

phosphate in a nearly saturated solution. A slight reduction of the acidity of the tissue fluid at a point in which the cartilage is in close contact with the circulation from the bone marrow reduces the solubility of these salts resulting in their precipitation. As a result of the foregoing work and also from the study of calcium phosphate concentration in the serum of rachitic infants, Tisdall and Harris tried to find the same fundamental principals applied to the deposition of calcium salts in the treatment of fractures. They found that in children from 4 months to 9 years there was 5.4 mg. of phosphorus to 100 cc. of blood serum and that in adults from 20 to 44 years, there were 3.8 mg. of phos. to 100 cc. of serum—a decrease of 1.6 mm. Studying adults with fractures, they found that the calcium content remains about the same but that the phosphate is increased from 3.8 mg. to 5.3 mg. This returns to normal at about 8 weeks after fracture. In two cases of non-union both the calcium and phosphorus were only slightly increased.

When a bone is broken a certain amount of tissue is damaged and more or less blood is extravasated, coagulated and autolysed. It has been shown experimentally that these substances can take calcium from the broken ends of the bone so that the soft tissues about a fracture are richer in calcium than normal tissues. It has also been shown that the phosphate content of the blood during the process of repair is greater than at other times.

These calcium, phosphate and carbonate ions are free in the acid medium; that is, they are in solution. With the growth of granulation tissue and the formation of the hyaline matrix of the newly formed trabeculae, these ions enter the trabeculae and become concentrated there. It must then be supposed that the hydrogen ion concentration within the trabeculae is lowered, that is, it becomes more alkaline. When this reaches a certain point below that of blood plasma, ionization occurs and triphosphorus calcium phosphate and calcium carbonate are precipitated as insoluble salts.

We may assume from the above study of fractured bone that the individual cell, the so-called osteoblast, has very little to do with bone production. Calcium salts are apparently deposited on the extracellular elements of connective tissue through some physico-chemical process. The fibroblast then becomes a bone cell. The periosteum with its areolar tissue and numerous small blood vessels is undoubtedly the best structure for bone formation, but it is not the only structure that may form bone as our study of extraskeletal bone shows.

It is an interesting observation that as far as we know, the processes of calcification and ossification are physico-chemically similar.

The only difference is that in the case of ossification, we are dealing with precipitation of these salts about living cells and with a free circulation in the immediate vicinity, while with calcification there are no living cells and there is no active circulation in the calcified bone.

4. From the gross, microscopic and physico-chemical findings we may summarize the process of repair of fracture as follows:

a. Immediate result of fracture is a hemorrhage which may extend into muscles, fascia and skin.

b. Organization of the blood clot occurs by ingrowth of connective tissue.

c. Calcium salts, calcium phosphate and calcium carbonate are deposited on the connective tissue stroma in the perivascular areas. These salts are carried in the blood system partly by colloids and partly by carbon dioxide. The change of the hydrogen ion concentration in the vicinity of a fracture with a decrease in the acidity apparently causes their precipitation.

d. The supply of calcium salts apparently comes from two sources; (1) from the circulating blood and (2) from the fractured ends of the bone by a process of demineralization and atrophy.

Discussion.

In our treatment of fractures, in addition to the purely mechanical replacement of fracture, we must attempt to influence body metabolism and to aid the repair of the soft tissues injured at the time of fracture.

Clinical deductions.—1. A fracture should be replaced immediately after injury. The delay awaiting the development of X-ray plates before reducing a fracture is often dangerous. The hemorrhage and resulting edema interfere markedly with attempts at replacement. In our physical examination of a patient with fracture, gentleness should be our first thought. Whenever we elicit crepitis, we increase hem-

orrhage and this interferes with reduction. Moreover, numerous attempts at reduction are apt to interfere with eventual union, as too much tissue destruction with the acid products resulting therefrom, delay the deposition of calcium salts.

2. Great care should be used in the application of retentive apparatus. Splints applied too tightly traumatize the soft parts and may cause muscle, nerve and vessel injuries. If the circulation is interfered with by too much external pressure the ingrowth of granulation tissue is hindered and ossification will be delayed. On the other hand if our retentive apparatus allows too great mobility of the fragments granulation tissue will be constantly injured and ossification interfered with. In the treatment of every fracture the first few days are the most important for success.

3. We should all pay more attention to the general hygiene of the patient. Sunlight and diet have been shown to be big factors in influencing the calcium and phosphate content of the blood. In certain cases of delayed union, yellow phosphorous, cod liver oil and calcium lactate have apparently aided osteogenesis.

4. Early active motion and massage by stimulating blood supply aid definitely the production of callus. Late adhesions of muscle, fibrosis of muscle and adhesions in joints following fractures are avoided.

5. Fractures in children differ essentially from those in adults in that anatomical displacements of fractured ends often unite without resultant deformity. In children, bone is much more pliable than in adults and fractures occur when bone growth is active. The studies of late results show that often where there has been over-riding of one to two inches, X-rays taken one or two years later show no shortening and it is often impossible to see the line of fracture. If we bear these facts in mind many unnecessary open operations on children will be avoided.

MENINGOCEREBRAL ADHESIONS

A HISTOLOGICAL STUDY OF THE RESULTS OF CEREBRAL INCISION AND CRANIOPLASTY

BY WILDER G. PENTFIELD, M.D., NEW YORK

From the Department of Surgery, College of Physicians and Surgeons, Columbia University, and the Pathological Laboratory of the Presbyterian Hospital

THE desire to cure or prevent traumatic epilepsy has led neurological surgeons to employ a bewildering variety of implants into dural and cranial defects. Drevermann (4) has summarized these efforts at some length. Widespread discussion of this problem particularly since the beginning of the war in 1914 has demonstrated great vagueness of thought as regards its underlying pathology. Experimental investigations of the viability of various transplants are plentiful, but careful histological studies are rare and studies of the process of "wound healing" in the brain still rarer. The following communication deals particularly with the mechanism of adhesions, changes in different types of neuroglia-cells being ignored for the present.

TECHNIQUE

One set of experiments was carried out on a series of dogs in the winter of 1922-23 approximately as follows: The lateral aspect of the cerebral cortex was exposed, with aseptic precautions, by turning down a large bone flap and excising the underlying dura. A similar exposure was then made of the opposite cerebral cortex. On the cortex of one side were placed a square of celluloid and a square of celloidin¹ side by side, held in place by a silk suture fastened to the margins of the dura. A puncture wound was made into the brain between the squares and in some cases wounds were made so as to be covered by the squares.

In the cortex of the opposite cerebral hemisphere a wound of loss of substance was made with a scalpel and squares of fat, excised dura and fascia placed, in order, over the wound and held there as though on a clothesline by a silk suture fastened to dura in front and back. A cuff of celloidin was folded about the margin of excised dura on one side or the other. Both bone flaps were then replaced and each fixed to the skull by

a silver wire bone suture, or silk sutures in the periosteum. In two of the ten animals in this series, decompression openings only were made, leaving the defect in the bone.

In the following year these experiments were supplemented by a second series of dogs. Either a bone flap was made on one side and decompression done on the other or a bilateral decompression was done. Stab wounds and implantations of strips of dura were made into the brain, or grosser wounds of the cortex were made and covered with sheets of fascia or fascia and fat which were sutured into the dural defect. Thus on most of the twenty animals used two separate operations were done each of which served as a control for the other.

One animal died with an operative infection and one on the second day from postoperative hæmorrhage. In one there was leakage of cerebrospinal fluid and this one was sacrificed early. The remaining 17 animals recovered perfectly after operation and were killed at different intervals up to 7 months by anaesthesia and perfusion of the carotid with 10 per cent formalin in normal saline solution.

The method of postmortem examination is of importance. If the skull cap be removed in the usual way or direct dissection be attempted, it is well-nigh impossible not to break adhesions between the brain and its covering. After the above fixation a saw cut was made parallel to the tentorium and just above it, and another slanting back and downward through the anterior part of the frontal lobes. When these two cuts met a wedge-shaped piece of skull and brain could be removed containing the field of both operations intact. In the case of a decompression a deep incision was then carried around the rim of the bone defect so that a cylinder containing brain membranes and muscle could be removed without disturbing the relations of these structures. The exact extent of ad-

¹Parlodion, Dupont.



Fig. 2. — Mallory's neuroglia stain. Longitudinal section of the tract of a ventricular needle passed into the ventricle 7 months previously. *c.t.*, Connective tissue in the tract. Empty spaces and rarefied tissue lined by a condensation of glia fibrils.

lesions could thus be seen in the gross and their nature studied in microscopic sections. In the case of bone flaps the brain was usually dissected away from the under surface of the cranial vault until the bone flap was approached. Then by gentle retraction the degree of adhesion and the nature of membranes between bone and brain could be made out and secured for section.

The blocks of brain with undisturbed coverings were embedded and cut in celloidin for the



Fig. 3. — Higher power photomicrograph of field drawn in Figure 2 to show the connective tissue core and surrounding glia condensation.

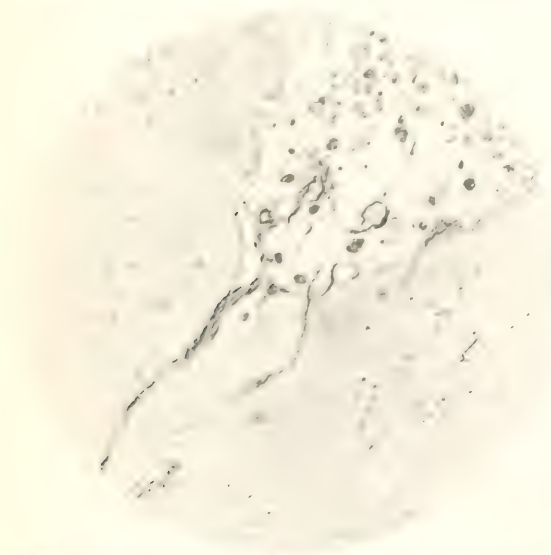


Fig. 4. — Deposition of Hemorrhoids and Valsalva. Bottom of laceration made with scalpel 7 months previously. Loose network of connective tissue in the tract and underlying brain.

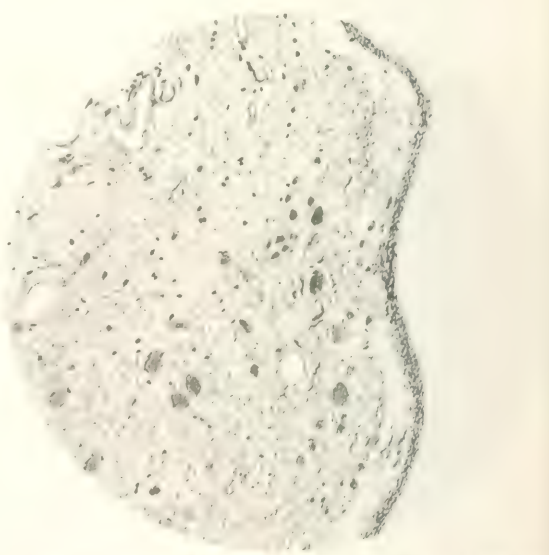


Fig. 5. — Case 3. — Mallory's neuroglia stain. Lining of empty tract left by passage of small ventricular needle 7 months before. Membrane of glia fibrils.

PENFIELD: MENINGOCEREBRAL ADHESIONS

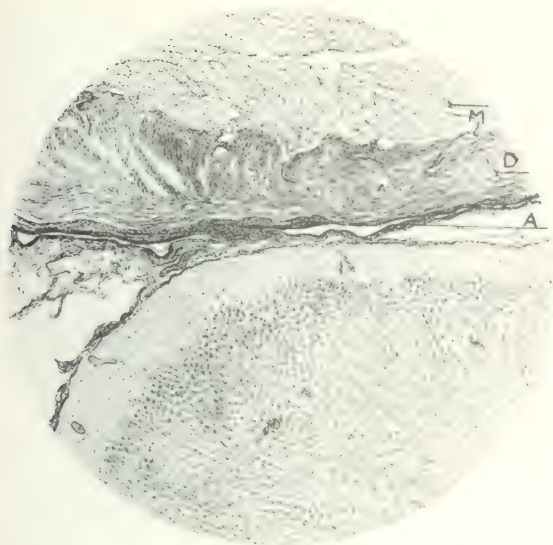


Fig. 5. Experiment 7. Hæmatoxylin and Van Gieson. The newly formed dura, *d*, 60 days after simple decompression, is free from arachnoid, *a*, except at one point.



Fig. 7. Experiment 13. Cajal's neuroglia method. Photomicrograph showing superficial gliosis and adhesion about small stabs, *s*.

most part. These sections were stained by Mallory's Phosphotungstic acid hæmatoxylin method for neuroglia, Nissl's method for nerve cells and Van Gieson and Mallory's methods for connective tissue. It was also found to be possible to cut good sized sections after freezing the properly fixed blocks. Thus blocks

were fixed in a solution of 15 per cent neutralized formalin and 2 per cent ammonium bromide. After the length of fixation called for by the different methods sections were cut from each block and the block returned to the fixative. Thus sections of the same block were stained by a number of different methods:



Fig. 6. Experiment 13. Achucarro's method, fourth variant. Photomicrograph showing conditions 02 days after decompression with removal of dura. Circumscribed adhesion to superficial gliosis, *g*.

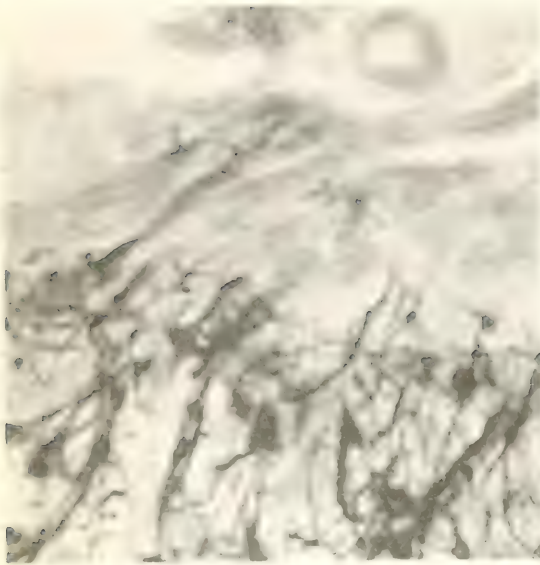


FIG. 4. Experiment 11. High power photomicrograph showing neuroglia stained by Ehrlich's Nissle's black. Dura unstained.

Cajal's gold-sublimate method (1) for fibrous and protoplasmic neuroglia, Rio Hortega's fourth variant of Achucarro's tannin method for neuroglia (3), Rio Hortega's silver carbonate methods (9, 10) for microglia and for fibrous and protoplasmic glia. It was possible to stain sections from these blocks by the hematoxylin and Van Gieson method and specific methods for fat as well.

BRAIN WOUNDS

Brain wounds do not heal in the sense of reproduction of parenchyma but certain progressive changes are observed. Six days after the removal with a scalpel of a small area of cerebral cortex, fibroblasts and a few new vessels were to be seen in the blood clot between the replaced bone flap and injured area of brain. There were also present numerous large round cells two to three times the diameter of a red blood cell (granulo-adipose cells or Gitterzellen). The cytoplasm of these cells contains many small round fat droplets as shown by specific fat stains. Occasionally the vacuoles are large and then the nucleus which is typically near the cell membrane is apt to be flattened against it. The cells may be seen at times on the outer sur-



FIG. 6. Experiment 7. Hematoxylin and Van Gieson. Low power photomicrograph showing the connective-tissue envelope which formed about a piece of celluloid placed between brain and temporal muscle 60 days before autopsy. The piece of celluloid has been removed from the slit.

face of blood vessel walls laden with fat droplets. Nineteen days after a similar wound this process of phagocytosis was going on actively and the nuclei consistently flattened against the cell periphery. These phagocytes are in reality microglia cells in an amœboid form as demonstrated by the Spanish investigator, Rio-Hortega. After several months some wounds, even deep ones as stab wounds, contained none of these phagocytic cells, if they may be called so, while in other cases they continued to be plentiful even as long as 7 months after a simple incision.

In addition to the formation over the surface of the brain of a new dura by fibroblastic proliferation, fibroblasts were early found in brain wounds themselves forming a loose network at the site of injury from which the brain elements were disappearing (Fig. 1). These connective tissue strands may be so sparsely scattered as to seem to be suspended in fluid (Fig. 2). Phagocytes may be present and a few vessels. At the surface such a network is continuous with the overlying dura. In Case 18, stabs were made with a cannula, the size of a small lumbar puncture needle, into the parietal lobe and the bone flap replaced. Four months after operation, on lifting the skull from the brain, thread-like cores about 1 centimeter in length attached to the bone were withdrawn from the holes. These fibrous threads (Fig. 3) seem to have a loose structure

when seen through the microscope, yet they are possessed of considerable tensile strength and, thanks to their firm attachment to the overlying fibrous meninx, must be capable of a considerable pull upon the brain tissue about the tract (Fig. 2).

If a narrow strip of dura is freed, leaving its base attached, and if the free end is then buried in brain, the condition at autopsy is found to be much the same, except that the dura strip retains its compact formation unchanged and completely fills the tract. Into rarefied areas along the tract a loose network of fibroblasts may be seen to pass from the implant.

As early as the sixth week after an incision, it is found to be bounded by a loosely interlacing layer of neuroglia fibrils. In Cases 9 and 10, 7 months after incision, there appeared a denser brush of neuroglia fibrils surrounding the areas of loss of substance. The deeper wounds were sometimes found to be represented by empty tunnels. In some cases the neuroglia fibrils formed a sort of superficial limiting membrane to the tunnels (Fig. 4); in others the membrane was more diffuse (Fig. 3). The cellular structure of the glia varied considerably. The layer of fibrils about the tracts of puncture wounds contained very few nuclei. Beneath this in many areas could be seen marked neuroglia hypertrophy and hyperplasia.

By means of differential stains for connective tissue and neuroglia, it was shown that some of the wound tracts were free of connective tissue and were in fact empty, while others contained loosely branching connective tissue which interlaced with a loose brushwork of glia fibrils.

Changes in nerve cells were absent even close to a brain wound. In some cases, however, evidences suggesting a destructive process were present even as late as the seventh month. Phagocytes were present in the neuroglia brushwork and adjacent nerve cells showed some tendency to chromatolysis. In experiment 11, five weeks after operation, Nissl stains showed next to each stab wound the usual narrow zone of tissue which stained faintly. In some sections the cytoplasm of neurones near this area stained faintly al-



Fig. 10. Experiment 10. Hematoxylin and Van Gieson. Membrane, *m*, which formed between celloidin and brain wound. Connective-tissue strands, *c.t.*, enter rarefied areas of brain and phagocytes, *ph*, are still present 7 months after operation.

though the position of the nuclei was normal. In other sections there was frank chromatolysis, some cells being swollen, with nuclei at the periphery and cytoplasm opaque.

A deep brain wound does not heal in the sense of healing elsewhere in the body. The neurones disappear about the injured area. There is apparently a long continued phagocytosis. Apparent condensation of neuroglia fibrils may take place and a cavity may result. Along the tract of injury connective tissue usually extends from the surface where it is continuous with the connective tissue covering the brain.

DURA REPAIR AND SUPPLEMENTARY ADHESIONS

Regrowth of a pseudomeningeal dura beneath a decompression opening has been demonstrated in recent experiments by Sayad and Harvey (11). As those authors point out, this has long been recognized by neurological

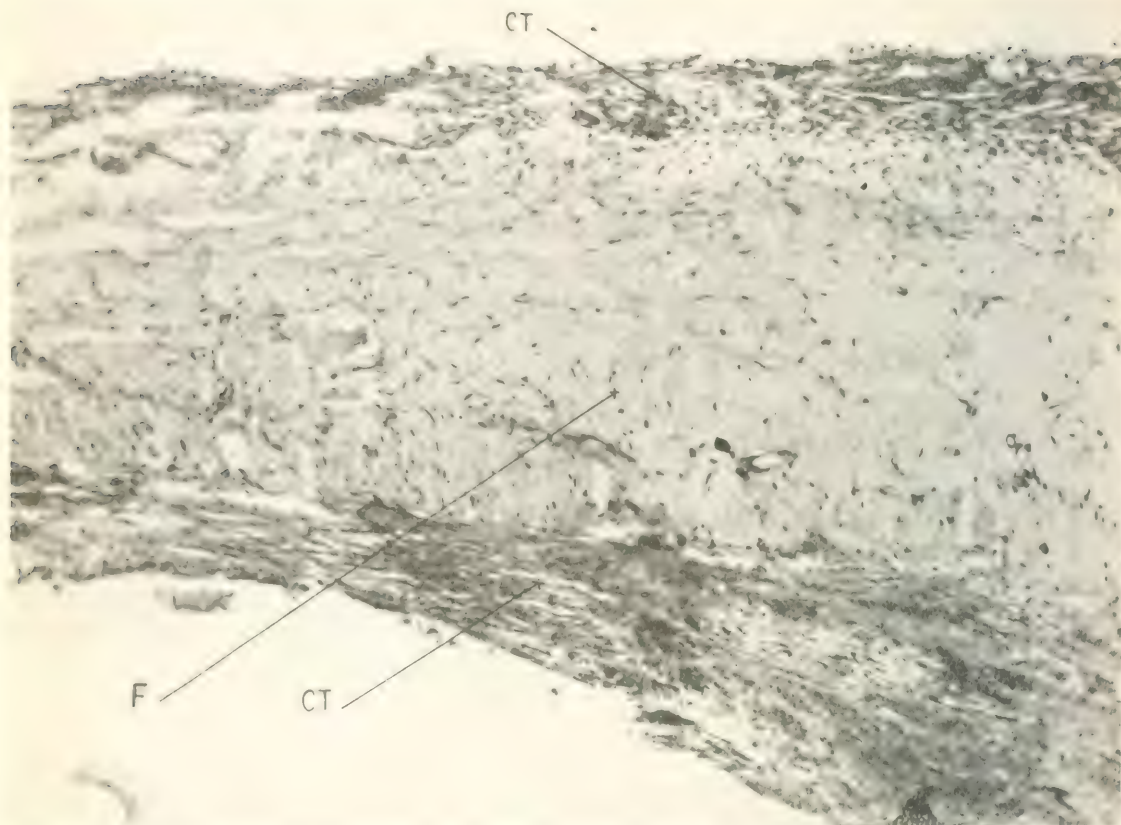


FIG. 6. (continued) Herndonville and Van Gieson. Trans-plant of fascia lata, *f*, to surface of brain beneath bone flap. Six days after operation fibroblastic layers, *ct*, already present on both sides.

surgeons. The growth of the membrane is rapid. It is not adherent to the underlying arachnoid (Fig. 5) and the cells with which it lines the sub-dural space resemble the arachnoid cells which line that cavity.

When a bone-flap operation is done the conditions are somewhat different. In the first place vascularization must come from the side or beneath, not from the covering. Also the factor of movement is largely eliminated. A membrane does form, adherent to the bone flap and free from uninjured brain. But it is much thinner than that which forms beneath the scalp and temporal muscle. The sheet of tissue varies a good deal being thicker over a laceration and much thicker over a foreign body.

If there has been injury to the brain, adhesions form, no matter what the covering. If

the injury is a gross one causing brain destruction the adhesions are composed of connective tissue strands entering the injured areas as described elsewhere in this communication. Adhesions however may occur in the vicinity of larger injuries or at the site of a very small superficial injury. The adhesion shown in Figure 6 corresponds to a circumscribed superficial gliosis (Fig. 6, G). There is no evidence of actual wound. Figure 7 shows a localized adhesion in the same case. Here a glia increase can be seen to center about a small stab and about this area the dura is adherent. Figure 8 shows the nature of the same adhesion more highly magnified. The connective tissue is unstained. The silver impregnation demonstrates the entrance of the neuroglia fibrils into the overlying connective tissue and throws light on the mechanism of adhesion.

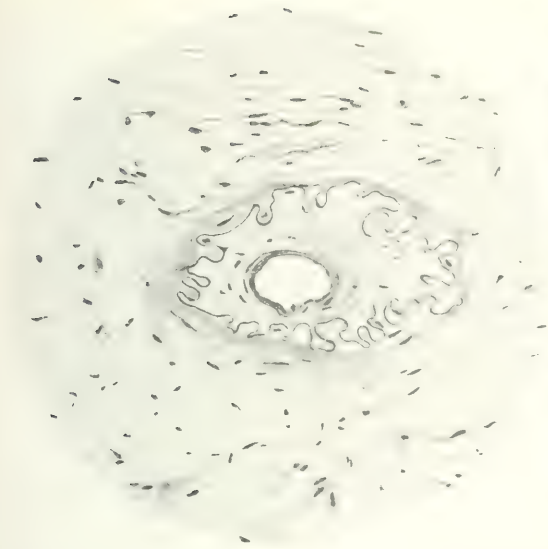


Fig. 12. Experiment 8. Canalization of thrombosed artery in fascia which had been transplanted to the surface of the brain four months before autopsy.

THE BRAIN UNDER FOREIGN BODIES

When a sheet of celluloid or celloidin¹ was placed over the intact surface of the cerebral cortex no changes were observed in the underlying neurones nor was there any evidence of a diffuse alteration in the neuroglia. In areas where the foreign body pressed upon brain as at an edge there resulted some thickening of the superficial layer of glia.

There was a response to the presence of the foreign body on the surface of the brain however. It was rapid and intense, but mesodermal in character. There formed a dense covering of connective tissue on all sides which, at the end of four weeks offered firm resistance to section and later seemed as hard as cartilage (Fig. 9). The connective tissue sheet opposed to each surface of celluloid was pearly white and glistening, the external sheet being adherent to overlying bone, in the case of a bone flap, or to muscle in the case of a decompression. The inner sheet seems to have left the arachnoid membrane intact although the pia-arachnoid spaces may at times have appeared to be obliterated by pressure.

¹This has been shown by W. C. Clarke (2) to be among the least irritating of foreign bodies.

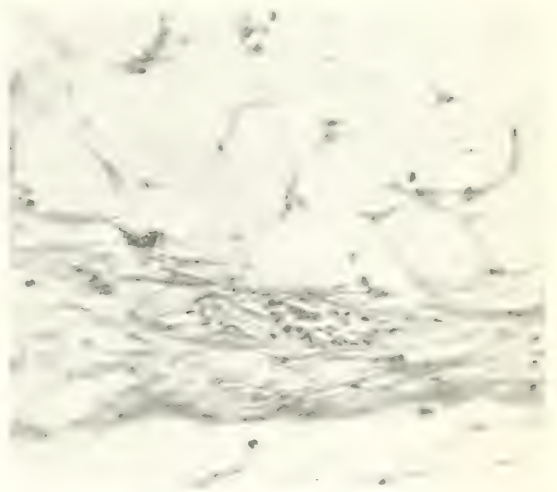


Fig. 13. Experiment 1. Haematoxylin and Van Gieson. Growth of fibroblasts beneath fat 6 days after it had been transplanted to surface of brain.

When a thin sheet of celluloid or celloidin is placed over a fresh brain laceration there forms rapidly, as described above, a dense connective tissue covering. The under covering (Fig. 10) is continuous with the connective tissue strands which pass downward into the laceration to interlace eventually with the neuroglia brushwork. The presence of the non-absorbable foreign body over the wound does not seem to alter conditions except that two dense sheets of connective tissue like a bursal cavity are substituted for the one layer of such tissue which would otherwise overlies the wound and be adherent to it and the coverings above. In the former case adhesion is direct between brain scar and skull or scalp. In the second a cavity is interposed. The reaction to celluloid seems to be about the same as to celloidin.

THE DURA—DURA TRANSPLANT

When fascia lata, fat or an excised piece of dura is transplanted to form the covering over a brain laceration there is rapid growth of new fibroblasts in the blood clot about the transplant, and down toward the laceration. There is, as a result, adhesion to the brain scar and to the overlying structure. A dense layer of connective tissue results, and in this layer can be recognized the fibres of the dura or fascia

transplant. External and internal to the transplant new parallel fibroblastic layers are laid down tangential to the brain surface (Fig. 11). The fascia lived, to judge from the staining reaction of its cells, and in several cases "canalized" arteries were found in the transplant (Fig. 10).

In cases where the fascia was sutured to the edges of the dural defect, the reaction was the same, the transplant became adherent to overlying covering and was densely fixed to any underlying brain scar. Such a transplant certainly does not prevent adhesions although in the absence of brain injury it may not form them.

When fat was used as a transplant or a fat-fascia sheet was sutured into the gap with fat next to the brain as is so ably recommended by Drevermann (4) and by many others, the result was the same. There rapidly formed new connective tissue all about the fat (Fig. 13). The amount of fat seemed to decrease and, in some cases of long standing, none could be found remaining.

SUMMARY

After a simple brain wound active phagocytosis continues over a long period and with it progressive disappearance of brain structure. Neurones adjacent to such an area of rarefaction may show chromatolysis as late as seven months after operation. Between normal brain structure and such rarefaction is found a brush work of neuroglia cells and sometimes a limiting layer of neuroglia fibrils. In the cavity is found a loose connective tissue network.

Deep adhesions are composed of connective tissue threads attached to dura, or its substitute, and to the glia brushwork at the bottom of the brain wound. Superficial adhesions result from slight injury and extend some little distance over the surface of the brain from the point injured. These adhesions are composed of an interlacement of connective tissue fibrils from the dura, with the fibrils of a superficial gliosis.

The thickness of the new or adventitious dura, formed after removal of the old, varies according to the available blood supply. Movement and foreign bodies are also factors

to be considered. The dura is thick after a decompression operation and thin beneath a bone flap. It is thicker over a brain laceration.

Placement of the least irritating foreign bodies, as celloidin, on the surface of the brain causes a very thick, hard connective tissue envelope to form all about it. The results are the same even when there is no wound of brain and when the foreign body lies beneath a relatively non-vascular bone flap. The layers of this envelope form a bursa-like cavity preventing direct adhesion to the scalp or skull. Adhesion between brain wound and lower layer of the envelope forms, of course, as well as adhesion between upper layer and skull or scalp.

Transplantation of various tissues to the surface of the brain is followed by rapid growth of a layer of fibroblasts above and beneath the transplant. Such procedures are useless if their purpose is to prevent adhesions, for fibroblasts grow wherever the conditions are suitable as do organisms in a contaminated wound. Thus the transplant is incorporated in the adhesion of brain to its covering.

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THE INFLUENCE OF A LOW ELECTROMOTIVE FORCE ON THE ELECTROPHORESIS OF LYMPHOCYTES OF DIFFERENT AGES.

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McCutcheon has reported (1) that small lymphocytes kept at 37°C. exhibit spontaneous movement which increases with the time that the cells are kept outside the body. McCutcheon allowed a drop of blood from the finger tip to spread between a glass slide and cover-slip. Then, surrounding the rim of the cover-slip with vaseline, he was able to study his preparation over a period of hours. The figures given in McCutcheon's paper show that with this technique the average spontaneous velocity of small lymphocytes increases from 4 micra per minute during the 1st hour, to over 10 micra per minute, reaching 15 micra per minute, after they were outside the body over 5 hours. McCutcheon does not state what direction of movement the cells took. Nor does he mention the changes in the blood film as a result of clotting or fibrin precipitation as a possible influence on lymphocytic movement. It would be interesting to note the velocity of movement during a period when the changes due to clotting are presumably at a minimum. This probably would be during the first 10 minutes of study, omitting, of course, the first movements during settling of the cells.

In 1922 a series of experiments were done to determine the influence of a low electromotive force on the movements of white blood cells, particularly small lymphocytes. The type of cell studied was similar to that studied by McCutcheon. A low electromotive force was used in order to compare with this electromotive force the electromotive forces passing between injured and relatively normal tissues. If these two could be compared, it could then be inferred that perhaps one of the factors which brings white blood cells to a point of injury may be this "current of injury." This has been discussed somewhat in detail elsewhere (2).

The cell in which the movements of the white blood cells were studied was constructed as follows:

Unglazed porcelain non-polarizable boot electrodes were set in a heavy glass slide, toe to toe, and then ground down so that the levels of the toes and glass were about the same. After placing a small drop of the uppermost layer of cells of centrifuged defibrinated blood on the glass block between the electrodes, a round cover-slip of 1 cm. diameter was placed over the drop which then spread out, just reaching the rim and simultaneously connecting the two electrodes. The edge of the cover-slip was instantly surrounded by a low melting liquid paraffin which solidified almost immediately. There was then ready to be studied on a specially constructed sliding warm stage at body temperature, a very thin film of blood cells in serum.

It is important to discuss some of the errors introduced by the use of an electrophoresis chamber of the construction described. In brief, the "true mobility" of the particles in suspension when under the influence of an electromotive force is the average mobility at all levels in the cell because of an independent flow of positively charged water near the glass surfaces (3). Since the cell is a closed system, there will necessarily be a slight anodal flow in the mid-regions of the cell. Thus, a negatively charged particle will be accelerated in the mid-regions of the cell and retarded near the surfaces of the glass.

A second flow of water within the system is caused by the charge on the water incidental to the presence of the porous porcelain electrodes. These electrodes permit the passage of water through the capillary spaces of the electrodes. Whatever the electrode's influence is due to, whether to the presence of a porcelain membrane, or, in addition, to a porcelain-protein membrane at the junction of the electrode with the serum, the water would be positively charged in relation to the membrane. That is, under the influence of a potential gradient there would be a cathodal flow of water through the system and across the field of observation, thus retarding the migration of a particle migrating toward the anode. For a more complete discussion of this subject the work of Briggs (4) and the numerous papers of Loeb in *The Journal of General Physiology* may be consulted.

In the experiments to be described, the lymphocytes studied were only those which moved in a nearly straight line across the field. The direction of migration was only toward the anode. *No lymphocytes at any level were ever observed to go toward the cathode.* The cells

studied were those in the mid-regions of the chamber, those resting on the glass hardly showing any "motility." Hence the figures in Table I are not the "true mobility" of the lymphocytes for the p.d. of 0.8 volt per cm. which was used, but they are approximations of velocity which may *not* be substituted in the Helmholtz-Lamb equation to determine the p.d. between lymphocytes and serum. The figures in Table I may be compared because of the large distances travelled, the constancy of technique, and the thinness of the film which made up the electrophoresis chamber.

TABLE I.

The Influence of an Electromotive Force of 0.8 Volt per Cm. (Current 1/25 Milli-ampere) on the Speed of Anodal Migration for Different Ages of Small Lymphocytes in Serum; Kept in Ice Box until Studied unless Used Immediately.

Age of lymphocytes.	Distance travelled.	Time.	Speed per min.
	<i>micra</i>	<i>min.</i>	<i>micra</i>
Used immediately.	185	15	12+
" "	180	14	12+
2 hrs.	210	15	14
2 "	260	15	17+
3 "	285	30	9+
6 "	410	34	12+
6 "	410	40	10+
6 "	410	31	13+
6 "	105	8	13+
30 "	205	12	17+
30 "	410	25	16+

The blood from which the lymphocytes studied were obtained, was drawn from the arm vein of a presumably healthy adult male, and after defibrination and centrifugation was kept in the ice box until used, unless the cells were studied immediately. In these same series of experiments no constant direction of migration was noted for polymorphonuclear leucocytes. However, Eliasoph (5) using platinum electrodes has noted that polymorphonuclear leucocytes, when studied in splenic tissue and gelatin suspensions, migrate toward the anode. From this work it would seem that polymorphonuclear cells are also negatively charged. Since this author used a compara-

tively high electromotive force, the magnitude of which is not mentioned in p.d. per cm., and since there was evidence of chemical change about the electrodes, these results cannot properly be considered in the theoretical considerations to follow.

With the exception of the 3 hour velocity and one of the 6 hour velocities, the speed of migration of the lymphocytes varied from $12+$ to $17+$ micra per minute. This variation is to be expected because of the experimental conditions. Therefore it may be considered that the length of time the lymphocytes were kept outside the body in serum in the ice box did not appreciably influence the speed of the anodal migration. It is quite interesting to note that the straight line velocity of small lymphocytes under the conditions studied is about the same as that reported by McCutcheon for "spontaneous velocity." It should be remembered that the increase in "spontaneous velocity" with time from 4 micra to 15 micra per minute was noted in McCutcheon's study of a whole blood film. The possible influence of clotting has been considered.

While the electromotive force was passing, lymphocytes in motion had practically always straight line motility (Fig. 1) and with interruption of the current, immediately ceased their movements. Or with reversal of the current they came to a dead stop, and immediately started to migrate to the new anode.

The question arises whether in the living animal tissues the electromotive forces which pass between injured and relatively normal tissues are of the same order of magnitude as the experimental electromotive force of 0.8 volt per cm. When the tissues are injured, the many physicochemical changes at the site of injury produce a system which makes the injured area electropositive (6). Thus the injured area may be considered similar to the anode and the direction of migration of the lymphocytes be correlated with the suggestion that the electromotive force is partially responsible for the cellular part of the inflammatory reaction as far as direction is concerned. Measurements of the "current of injury," of course, have not measured the p.d. between cells which were normal and injured, but have determined rather the p.d. between fascial plane and injured muscle or nerve (6). Hence, although electromotive forces of 0.08 volt have been reported, the actual p.d. per cm. between the injured and

uninjured tissue is not known. Since some cut surfaces have been found to be (by the authors cited above (6)) at about the same electrical potential as the uninjured fascial surface at the moment after cutting, it may be inferred that the difference in potential between injured and uninjured tissues may be of a somewhat similar order of magnitude as that measured between fascial surface and injured surface. The many changes in physicochemical make-up of injured

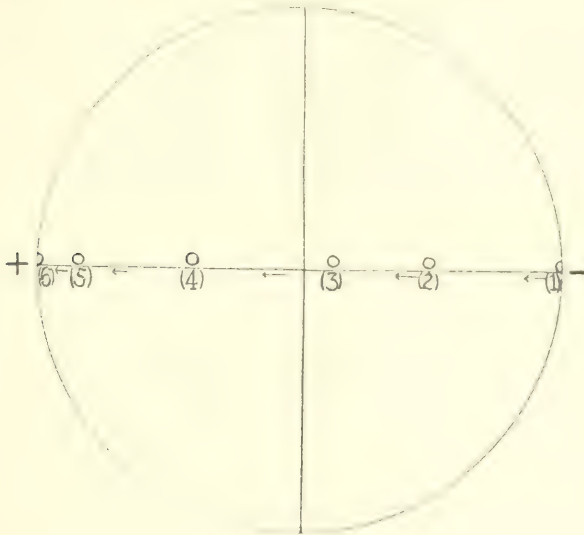


FIG. 1. Schema to show course of lymphocyte and method of determination of speed. Diameter of field 410 micra. Cross lines on eyepiece. Lymphocyte entered field at (1), time 4:01, was at (3) at 4:11, and crossed out of range at 4:35 (6). The straight line movement was occasionally slightly above or below the line in other determinations but in general was similar to the migration depicted in the figure. The time taken to migrate 410 micra was 34 minutes. In this experiment therefore, the mean rate was $12 \pm$ micra per minute.

tissues most probably produce a difference of potential between limiting border of the zone of injury and the *nearest* relatively normal cells of at least 10 millivolts. If the nearest relatively normal cells are 1 mm. away, the P.D. per cm. would be 100 millivolts or 0.1 volt per cm. This would place the electromotive force used in these experiments in the same order of magnitude as those existing in living tissues.

SUMMARY AND CONCLUSIONS.

1. Small lymphocytes in serum at 37°C. migrate toward the anode under experimental conditions described.

2. The electromotive force of 0.8 volt per cm. under the same conditions produced a straight line velocity which approximated that reported by McCutcheon for spontaneous velocity after his preparation had been studied over 5 hours.

3. Keeping the lymphocytes on ice up to 30 hours did not produce an appreciable difference in velocity of straight line migration from that speed determined if the cells were studied immediately.

4. The possible relationships between the type and order of magnitude of the electromotive force passing between injured and normal tissues and the electromotive force used experimentally are briefly discussed.

The author desires to express his sincere thanks to Professor H. W. Farwell of the Department of Physics, Professor H. B. Williams of the Department of Physiology, and Professors W. C. Clarke and A. P. Stout of the Department of Surgery, for the many courtesies given him during the course of this work.

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COMMON SURGICAL PROCEDURES*

THEIR SCIENTIFIC STATUS IN CANCER

WILLIAM C. CLARKE, M.D.

NEW YORK

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There have been many epochs in the study, the practice, and the progress of medicine. Many of them, as you know, shade one into the other. Every age apparently fools itself into thinking that it has knowledge of and can do much for the various diseases from which people suffer. Each age, looking back, is amused with the status of treatment in the past; to us many of the procedures used at the time of John Hunter seem very bad indeed when compared with those of the present, and many of them certainly were bad. Yet Hunter was a man of keen perception, and although he lacked a conventional education, he did things. He did not agree with everyone, for he was one of those rare individuals who was not moulded by the habit of the times as to method of procedure.

Knowledge in the pure sciences rests for the most part upon a strong scientific basis. Is this true in medicine? Faraday proceeded in his researches in magnetism and the electrical current from observation to observation. Each research worker claims that he does this likewise. But apparently the accuracy—accuracy as evaluated by the test of subsequent findings—of observations is determined by the character of the human emotions of each research worker. Similarly habit creates standards in responses to emotions in research. In the present knowledge of dynamics, the research worker proceeds on what is apparently the firmest foundation yet known. The observations of Clerk Maxwell, Eddington, Milliken, Steinmetz, and many others, are as little colored by their wishes and superstitions as were Faraday's. Einstein in his mathemati-

cal applications may be as little hampered by his emotional wishes, which time alone will evaluate, since the future test of experience is the only test possible to man. Jacques Loeb in his researches apparently attempted to escape from the present standard established by habit of thought in biology interwoven as it is by dialectic argument and by the processes of thought of each biologist. Loeb attempted to place biology on the foundation of pure science. He attempted to escape from the present day, three-dimensional concepts and from the satisfying terms of present day biology, "the genes", "inheritance", "environment". He seemed to realize, as has Thompson, that why a thing happens and how a thing happens are but questions of the human emotions, the truly philosophical statement is—things happen. He seemed to realize as apparently did Darwin, as did von Helmholtz, as did Kant, as did Descartes, and as does Einstein, that man can only make his observations of happenings—questions are probably but figments of the human mind, therefore, strictly speaking, there are no answers. The scientist in all branches of knowledge, therefore the scientist in medicine, can but make observations. Dynamics, manifest to man, as light, electricity, and other modes of energy, apparently must be placed on a similar dimensional basis in all fields. True observations can not contradict observations. If the physicist discovers that light, as he observes its phenomena, presents conflicting observations on a three-dimensional basis and does not contradict on a four-dimensional basis, he naturally accepts the latter until still other observations are made. Thus Newtonian physics have been accepted until they have be-

* An address, revised for publication, delivered before the Brooklyn Pathological Society, October 8, 1925. From the Department of Surgery, College of Physicians and Surgeons.

come a fixed habit of thought. The "law of gravitation" has permeated all teachings until the present time, when, through the disturbing questions of the relativist, the bitterly sharp needle of doubt has punctured his complacency one of the strongest formulas of man. In spite of comfortable habit, in spite of superstition, observations must be constantly rewritten if man is to make progress. Otherwise, except as a means of amusement, all his tremendous effort in research is wasted.

In medicine, procedure, if it be followed because it is custom which is handed down from former times, is not progress. If the observations of the biologist rest alone upon the three dimensional observations of the morphologist and do not take into account the many dimensioned fields into which the pure scientist is reaching, is the biologist making the most of progress? The morphologist makes progress when he makes observations on the fixed and stained cells, when he counts the chromosomes of the germ cells, when he observes the cell and its nucleus—but must not these observations be constantly evaluated, integrated with observations in all fields of science, if there is to be real progress? In clinical medicine the same evaluation of observations must be constantly made as in all sciences. The objection is at once raised that this evaluation of observations is impossible. The answer is that if fixed habit of thought, custom, and superstition were cast out of medical procedure to the degree with which it has been cast out of many of the branches of pure science, the present degree of progress in clinical medicine and surgery would not be as open to criticism as it is at the present time. History reveals that such fixed habits of thought in procedure in surgery obstructed the acceptance of the observations of Lister—observations of infected wounds which he attempted to integrate with the recently made observations in bacteriology. Karl Pear-

son has well pointed out in his "Grammar of Science" as has H. Poincare in his "Value of Science", the possibilities for progress and the difficulties.

At present it seems as if procedure in the treatment of cancer were following a pathway of habit. Observations on procedure in medicine can only be evaluated by comparisons. In this attempted evaluation of the present-day procedure in cancer, I have selected cancer of the female breast as a thesis. A good many of you who are surgeons operate on cancer of the female breast, feeling that you prolong the patient's life by your procedure. You know well with what enthusiasm you rush off of a morning to your hospital to excise cancer after cancer. How do you know whether you prolong life or not, and you probably do, for the report of the English Ministry of Health would seem to indicate that three years is added to life by the complete operation in cancer of the breast.

If you have a few patients alive ten years after operation, that by clinical and microscopic examinations were believed to be cancer cases, you are proud. If you have a couple more who have lived for fifteen years you are tickled to death. Few of you know of a patient who, after twenty years have elapsed, is apparently cured. This must mean that you are not so confident that your operation is doing so much to help your cancer patients. When you commenced you entered into the combat with cancer with zest, for had you not been taught as students that it was best to operate on cancer? You accepted the procedure as a matter of course. However, as the years passed, and your friends, maybe some of your relatives, dropped off one by one, dying of cancer after operation, you began to doubt. In fact, if operation "cured", taking into account the natural life expectancy, there would be plenty of cases alive many years after the onset of their cancer. Are you curing any? As to the use of the word "cured". The man in

the street asks right away, as John Hunter and many others have asked, "What do you mean by 'cured'?" Hunter said in the eighteenth century, regarding cancer—

No cure has yet been found; for what I call a cure is an alteration of the disposition and the effect of that disposition, and not the destruction of the cancerous parts. But, as we have no such medicine, we are often obliged to remove cancerous parts; which extirpation, however, will often cure as well as we could do by changing the disposition and action. Arsenic seems to have power of this kind, and its effects might be increased by being used internally and externally, but its use is very dangerous, and I am afraid insufficient for the disease. This is a remedy which enters into the empirical nostrums which are in vogue for curing cancer; and among which Plunkett's holds the highest rank. But this is no new discovery, for Sennertus, who lived the Lord knows how long ago, mentions a Roderigues and Flusius, who obtained considerable fame and fortune by such a composition. I was desirous to meet Mr. Plunkett, to decide on the propriety of using his medicine in a particular case; I have no objection to meet anybody; it was the young one; the old one is dead, and might have died himself of a cancer for aught I know. I asked him what he intended to do with his medicine. He said, "To cure the patient." "Let me know what you mean by that: do you mean alter the diseased state of the parts or do you mean by your medicine to remove the parts diseased?" "I mean to destroy them," he replied. "Well, then, that is nothing more than I or any other surgeon can do with less pain to the patient." Poor Woollett, the engraver died under one of these cancer-cures; he was under my care when this person took him in hand. He had been a life-guardsmen, I think, and had got a never failing receipt. I continued to call on Woollett as a friend, and received great accounts of the good effects; upon hearing which I said, if the man would give me leave to watch regularly the appearance of the cancer, and see myself the good effects, and should be satisfied of its curing only that cancer, (mind, not by destroying it), I would exert all my power to make him the richest man in the kingdom. But he would have nothing to do with me and tortured poor Woollett for some time; till at last I heard he died. (1)

There is also another chapter in the story and that is this: how do you know you are dealing with cancer? You know, for instance, that cancer of the

tongue is very vicious. I do not believe you know many patients with that disease who live very long after operation. There is a man still living after fifteen years. I saw him, alive and well, six months ago. Is he not a surgical curiosity? A wedge was excised from his tongue in 1910. Dr. William H. Welch stated at the time of the operation, after seeing the slide, that there was no doubt about the diagnosis, the only question being, should the surgeon have taken out the entire tongue and regional lymph nodes? Other pathologists also agreed at the time that it was a straightforward cancer of the tongue, a squamous cell epithelioma. When visitors call from out of town, I always show them that slide. They agree on the diagnosis, until I tell them the man is alive and that the operation was performed so many years ago. Then they vacillate and say, "Well, I don't know, maybe it is not an epithelioma after all." What does that mean? It means that those looking through the microscope do not know so much about what they are looking at as some of you are led to believe. That is my honest opinion. I realize the fact that the microscope only lends itself to seeing a little of the cellular form at the moment and when we add the subsequent clinical history we often begin to wonder about the diagnosis.

Rodman, in 1815, has well stated the reasons for confusion among clinicians as to whether operation for tumors of the "mammar" is advisable.

"There is no part of practice about which less has been satisfactorily established, than the extirpation of the mamma when it contains an induration. The professional enemies to the operation are numerous, and so are the friends; and each one affirms that his opinion is the result of practice. How is it possible that such contradictory opinions have prevailed so long amongst men of high character? The truth is, the reasons on both sides may be upright. A surgeon who amputates the breast of a great many females, for movable tumors, of a moderate size, has many chances to be successful when there is no other danger to fear for some time, but the irritation and fever occasioned by the operation. And while

(1) Paget, Stephen; John Hunter, N. Y. Longmans, Green & Co., 1898, Page 109.

he is inclined to extirpate all he meets with, he has little opportunity from his own experience, to witness how many cancers can be effected without the knife, or to know how remedies can be used for that purpose. His opinion, therefore, will be decidedly in favor of amputation. Whereas the surgeon who carefully watches all the circumstances, sees the ruinous consequences of such operations on the female constitution, and observes that the number of diseased females is greater who survive without cutting, will speak according to the dictates of his experience. In this way, the opinion of both surgeons may proceed from the most upright intentions; yet the former approving from practice and disapproving from ignorance, and the latter, approving and disapproving from the conviction impressed by observation, while neither of the parties possesses clear or distinct ideas on the subject.

"But it might be said that such a state of things could not continue long, since one of the two opinions must soon prevail. And this would certainly happen, were not mankind fonder of premature induction, than of wary and persevering investigation. Though each party claims the superiority of his opinion, both submit to the decision of inconclusive arguments, by supporting the mistakes which render every opinion, comprehended in the current theory of cancer, indisputable." (2)

A process which does not take life may be diagnosed "cancer" and treated successfully, for any treatment may be successful in a benign growth. This statement unfortunately is a platitudinous as is the statement in the campaign notes of the American Society for the Control of Cancer, of September, 1925: "If, while cancer is small, it is completely removed by surgery or destroyed with x-rays or radium, or in fact, by any other means, that is an end of it. This could not be so if cancer were a disease which affected the whole body." The quotation above from John Hunter, written nearly two centuries ago, shows a somewhat different point of view, but do not the results of modern operative treatment indicate that his conception was as near the truth?

These remarks as to procedure in cancer must not be taken as disparaging the epoch-making advances which have

taken place in medicine and surgery that would be a revelation to the great clinicians who lived before 1870. The good is overwhelming which accrues to patients from such efforts. Anyone who has had an acute attack of appendicitis, who has been operated upon by an able surgeon in an up-to-date hospital and has returned in two weeks to his occupation, cured as far as the suppurative appendix is concerned, need but compare his circumstances with those of the miserable patients previous to thirty-five years ago, to be satisfied as to the benefits of modern surgery. The high mortality of fifteen to twenty-five per cent from puerperal sepsis in lying-in women in a hospital previous to the teachings of Semmelweis and others was obvious to all, and when this mortality is compared with the less than one-hundredth of one per cent. mortality of the present day, there are no doubters as to the efficacy of the aseptic technique of the present-day obstetrician. There is little if any doubt as to the benefits derived from such procedures, but such unanimity of opinion in the treatment of surgical processes only obtains where comparisons of results of the treated and untreated are easy and therefore obvious to all clinicians.

Where comparisons are difficult to make, and the results of treatment are not obvious, history shows that habit of mind decrees that in procedure there be a beaten path to be followed whether for good or evil. Most surgeons of pre-antiseptic days regarded a cancer as a local process and therefore eradicable. Tissue destructive pastes were tried, because without anesthesia and with wound sepsis rampant, few patients submitted to even limited operations for the attempted removal of growths. Given anesthesia and aroused to the possibilities of asepsis, surgeons buckled to their work in the laborious cutting away of cancers from both superficial and deep organs. A maze of operative procedures were planned during the lat-

(2) Rodman, John: *A Practical Treatise of Cancer of the Female Breast*. Pathol., London, 1763.

ter part of the last century. Unfortunately, comparisons are difficult to make as far as determining the benefits which accrue from treatment, since cancer may kill in a year or in twenty years. At the same time the question of cure must not be confused with whether a particular form of treatment prolongs life or not.

I have with me the statistics of the follow-up work of the Presbyterian Hospital in New York City, from 1910 until 1924. These patients were cared for by a large group of surgeons, among them Dr. Joseph A. Blake and Dr. George E. Brewer.

CANCER OF THE BREAST

OPERATED UPON AT THE PRESBYTERIAN HOSPITAL

October, 1924-October, 1924	420 cases
Not followed	135
Operative deaths	11
Total not analyzed	143
Cases followed up to 1925	264
Alive, 100—42% (av'ge post op. life, 50 mos.)	
Dead, 164—58% (av'ge post op. life 24.3 mos.)	

Distribution of 264 cases followed in decades according to age at time of operation.

Age at operation	25-34	35-44	45-54	55-64	65-74	75-84
Total cases alive	4(38)	26(54)	41(60)	19(51)	9(55.8)	1(43)
Cases alive in 1925	1(20)	18(53)	29(68.4)	8(64)	1(45)	
Dead	10(19.8)	49(32.1)	59(28.9)	36(22.9)	7(38.8)	1(33)

From these 288 cases followed from 1910 up to 1924:

One has lived fifteen years. Cancer right breast. (Nine years later cancer in left breast.)

One has lived fourteen years.

One has lived twelve years.

Two have lived eleven years.

Two have lived ten years.

And these nine patients are still alive and well in 1925.

These figures must be taken with caution since the bulk of the patients lost sight of are those operated upon in the earliest part of the 14 year period from 1910 to 1924. Therefore, the 288 patients operated upon whose histories

are known are from the latter portion of the period. There may, of course, be patients who are alive and apparently well among those lost sight of. In substantiation of this, Dr. Jonathan M. Wainwright, of Scranton, Pennsylvania, has kindly shown me his statistics of cancer of the female breast from 1901 to the present time. He has performed a complete operation upon sixty-eight cases and he has continuous records of sixty-seven of these patients. There is one patient who is now in her eighty-eighth year showing no evidence of re-appearance of cancer. She was operated upon in her sixty-sixth year, twenty-one years ago. The section taken from her tumor at the time of operation shows what the majority of microscopists call cancer and at the time of operation, axillary involvement. There are two others, alive and apparently well in 1925, operated upon fifteen years ago, at the ages of thirty-eight and forty-nine, respectively. Dr. Wainwright pointed out that another twenty years must elapse to determine

the outcome among his cases most recently operated upon which make up the bulk of his sixty-seven cases. Another point in these figures to be considered is what the criterion is of a malignant growth or cancer in any particular hospital; for, as Rodman pointed out over 100 years ago, if a few benign growths creep into the records, comparisons of procedure will show different results from comparisons where only "cancers" are included. At present in this 14 year period, 252 cases of supposedly benign growth of the female breast have been operated on and though the follow-up on this group is as yet very incomplete, there are but two cases which subsequently suggest that an error had been

made in either the clinical or microscopic findings. Later, a more complete report, it is hoped, may be made in order to standardize more accurately what is to be called a cancer and what a benign growth at the time of operation.

I shall compare these statistics with statistics, meager at present it is true, of cancer of the breast not operated upon, in the hope of determining the actual lengthening of life, if any, that operation has brought. We have been making an effort for the sake of comparisons to discover how long a person lives who has a cancer of the breast that is not operated upon, or who receives no treatment.

SUPPOSED CANCER OF THE BREAST CASES NOT OPERATED UPON

Thirty-eight unoperated cases obtained from a questionnaire sent to 1,500 graduates of the P. and S., 1900 to 1909 inclusive, and to others.

Distribution in decades according to age at reputed discovery of tumor.

Age	25-34	35-44	45-54	55-64	65-74	75-
Number of cases	2(21)	6(34)	7(34)	12(36)	6(26)	5(75)

Figures in parenthesis indicate the average duration of life in months after reputed discovery of tumor.

Of these cases which are dead, nine were treated with X-ray more or less extensively and two were treated with radium, but all for the most part were treated late in their disease as a palliative procedure.

There were over seventy-seven cases turned in but only forty-two measured up to a clinical history which made cancer probable. For example, a persistent ulcer of the breast appearing in a tumor which later invaded the axilla with swelling of the arm and accompanied by some clinical evidence of metastasis followed by death seemingly in connection with the above signs, was probably a cancer, even though an autopsy was not obtained.

Many more histories must be obtained before any deductions are possi-

ble from such observations. Several features should be indicated. Of these cases dead of apparent cancer, two lived five years, one lived six years. There is still another very typical case, not as yet included in the above statistics who lived eighteen years. It is also worthy of mention that some of the above cases had masses in their breast, when discovered, too large to warrant operation, yet the length of time these patients lived is estimated from their reputed discovery of their growth. This procedure must be followed since it is the one followed in the group of cases operated upon. Apparently an interval, varying

from one week to several months, elapses between discovery of their tumor and when they ask medical advice, as occurs in those cases which seek operation.

As many of you know, Lazarus-Barlow 3, in England, has collected case histories of cancer of the female breast in an attempt to learn the expectancy of life and in the hope of obtaining a basis for comparison as to the various methods of treatment. In regard to his statistics, he points out the difficulty in determining when the cancer actually commenced and he feels that the mean duration for length of life in his cases of cancer of the breast may be overestimated, but he writes "nevertheless, it appears certain that some cases of

(3) Lazarus-Barlow, W. S. "Natural Duration of Cancer". Brit. M. J. vol. 2, (Aug.) 1924.

malignant disease last for a very long time." His statistics for cancer of the breast are:

cases should be operated upon and which should not be so treated. For curiously, some of the cases benefited

Age	Sex	No. of cases	Natural Mean.	Duration Maximum	Duration Minimum	Percentage of cases below Mean.
Under 25	F.	1	24.0			
25-34	F.	15	36.0	196	3	80.0
35-44	F.	42	32.0	112	5	64.3
45-54	F.	61	39.2	186	2	68.8
55-64	F.	60	40.7	210	3	70.0
65-74	F.	44	44.3	169	11	63.6
75 and over	F.	20	36.1	64	12	50.0
Total cases		243	38.4	210	2	59.3

It should be noted that the maximum length of life of some of these patients is greater than those cases which were operated on at the Presbyterian Hospital as shown above.

Today there is much propaganda published to persuade people to be operated upon at once on the discovery of a tumor, and by frequent physical examination, to make the discovery earlier than in the past. At the same time, much of this propaganda is misleading, the truth is hidden and distorted. The efforts of collecting the follow-up results on operations for cancer will be wasted unless comparisons are possible so that the whole truth may be known. It is true that there has been more intensive research work in cancer than in almost any other field of medicine, more intensive research work in cancer than in almost any other field of medicine, but will not these workers be more effective if they are not lulled into complacency believing that the operation for cancer is effective?

I believe that the total good which accrues to all patients when all forms of cancer are considered is disappointingly small. I believe that operation makes the majority of cancer cases more comfortable for a period, and affords them a brief mental uplift, unfortunately counterbalanced by the almost inevitable reappearance of their growths. I believe that in a few cases, the good is overwhelming, therefore I believe all should be operated upon and as early as possible, until a better procedure be discovered, or until it be discovered which

apparently by operation, showed both clinically and from a gross and microscopic study large and far advanced cancer. One of the longest lived breast cases in the Presbyterian Hospital group presented a large tumor and an axillary lymphnode at least three centimeters in diameter at the time of operation by Doctor Darrach. The axillary lymphnode showed an extensive involvement with cancer similar to that noted in the breast. Patient G. A., aged fifty, with a history of one year referable to his stomach, suggesting either an ulcer or cancer, was operated on August 6, 1919, by Dr. A. V. S. Lambert. A partial gastrectomy was done. Presenting into the lumen of the stomach, there was a large cauliflower mass, five by eight by four cm. Its free surface was ulcerated. There were many enlarged lymphnodes in the mesentery. Microscopic examination of the tumor showed an extensive and a typical proliferation of epithelium, suggesting gland formation. Mitoses not frequent. Lymph nodes examined which were removed showed no cancer. This patient seen December 5, 1923, six years and three months after operation, has had no gastric disturbance, is apparently well, and continues his daily work without interruption.

The data presented above referable to cancer and the operative procedure suggest much work that may be done in the collection of cases which have been operated upon and those which have not been. The above statements are merely my beliefs at the present time. If it is

from that at present the surgeon is enthusiastically, laboriously operating on cancer after cancer from habit, traveling the wrong road, the economic loss in hospital facilities and loss to the patient should be considered. Many medical men regard these remarks as destructive criticism and lacking any constructive suggestion to aid in the cancer problem. There are many leads which appear constructive; certainly the study of inheritance factors as carried on by Maud Slye in the breeding of white mice should not be lightly cast aside by the "authorities" as not applicable to man. Certainly as she has repeatedly pointed out, they fail to grasp the full implication of her work, and that her selected breeding experiments point to the fact "that the thing which is transmitted in the heredity of cancer is the tendency of a given organ or organs to yield to cancer". She is dealing with a unit characteristic which is recessive. The question is not whether the mouse cancer is the same as the human cancer, but rather that the tendency or susceptibility to the development of cancer or an apparently similar lesion as seen in mouse and man, can be determined by selective breeding. She believes that what is true for the selected breeding of peas and beans is as true for mice and men. The statement is often made that there is no evidence that cancer is inherited in man. Maud Slye has never claimed that her mice, as she has bred them, have inherited cancer one from the other. To inherit or transmit a sex-linked recessive tendency to develop a thing is not inheriting a disease or active process, be it tuberculosis or be it cancer.

C. C. Little has written from the Department of Genetics, Carnegie Institute of Washington, "The Work of Murray (1908), Haaland, (1908), Tyzzer (1909) and Slye (1913), have shown that a predisposition to the formation of cancer is inherited in mice. The exact type of inheritance is still a matter of debate although the weight of evidence points in the direction of a complicated Mendelian inheritance

of many factors as the underlying causes. From the outset it should be made clear that inheritance, in the direct sense of transmission, is not involved. It is rather that certain individuals inherit a tendency towards unbalanced growth, following irritation from either internal or external causes, of various parts of the body. That such a predisposition is inherited in mice is beyond question.

"From the evidence, we may conclude that there exist in man one or more hereditary tendencies to the formation of malignant neoplasms. The fact of inheritance is clear but the type of inheritance needs further investigation. It does not appear to be simple Mendelian inheritance. This does not, however, conclude the possibility as it will be found to be dependent upon multiple Mendelizing factors."

As Slye and others have shown, in mice at least, cancer susceptibility of particular organs is transmitted as a unit characteristic. If the causes of death in man are more accurately determined, and susceptibility to cancer of stomach or cancer of breast has occurred in the families of those intermarrying, certainly it is important to add to the present day propaganda for annual examination, the suggestion that particular organs should be kept under more careful observation than is done at present.

Finally, a field of research is suggested in that the maternal and paternal tumors from selected cancer strains should be partitioned and introduced into recently born mice of these cancer parents, doomed because of their inheritance to die of cancer. It is suggested that this field of research, as outlined, may reveal that the inherited susceptibility to develop cancer is changed in these offspring to insusceptibility, and cancer does not develop. If this experiment is undertaken by many different workers, if there be any merit in the suggestion, it will be revealed.

In conclusion, these remarks are really meant to stimulate a reevaluation of present day procedure and to indicate the necessity for comparisons in all fields of science, particularly in medicine.

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**PROGRESSIVE GANGRENOUS INFECTION OF THE SKIN AND
SUBCUTANEOUS TISSUES, FOLLOWING OPERATION
FOR ACUTE PERFORATIVE APPENDICITIS**

A STUDY IN SYMBIOSIS

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AND

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THE object of this communication is to report the histories of two cases of extensive destruction of the skin and subcutaneous areolar tissues, from infections occurring in the operative wounds of cases of acute perforative appendicitis.

While all surgeons are familiar with the various types of wound infection, following operations on septic conditions of the various abdominal viscera, necessitating contamination of the wound surfaces during the operative procedures, or following the drainage of these septic foci; few such superficial infections give rise to serious apprehension, when the intra-peritoneal focus ceases to extend, and progresses normally toward recovery.

In practically all such cases, it is the deep-seated primary intra-abdominal infective process which causes anxiety; and not the superficial secondary stitch abscess or subcutaneous cellulitis, for these almost invariably are controlled by the simple procedure, of removal of sutures and establishing drainage of the subcutaneous space.

In the cases which I am reporting here, the opposite of this condition prevailed, and persisted to such an extent, as to give rise to the greatest anxiety.

The progress of this infection was not rapid, as in a post-operative erysipelas, a streptococcus cellulitis, or gas bacillus infection; nor was it associated with high fever and grave toxæmia usually present in these acute conditions. It was on the other hand, exceedingly slow, extending only one or two centimetres in the course of a week or ten days, and with little or no fever or evidences of toxæmia. This type of infection seemed singularly rebellious to any and all kinds of ordinary wound treatment. It was apparently uninfluenced by local incisions, drainage, irrigation, heat, cold, Carrel-Dakin technic, or by the employment of other chemical disinfecting agents. It was not benefited by sunlight, Alpine light, or any other form of radiant energy.

The process may perhaps best be described, as a slowly advancing white subcutaneous slough. The skin lesion, occurring somewhat later, appeared at first as a deep red or purple superficial edema, which later slowly broke down into a necrotic mass resembling an untreated carbuncle. This in turn was surrounded by a zone of lighter colored erythema, which gradually faded out into the normal skin. At times the subcutaneous necrotic area and cutaneous margins would assume a dark gray, or even black color. Beneath the

* Read before the American Surgical Association, May 26, 1926.

sloughing area, which varied considerably in extent, sometimes being limited to the upper third of the subcutaneous fat, and at others extending well down to the deep aponeurosis; there was always a layer of granulation tissue, which seemed to be a definite but ineffectual effort of repair.

In both of my cases the process seemed to start at the upper part of the cutaneous wound, and gradually crept downward along both margins toward the site of the intra-peritoneal drain opening. The actual site of the deep drainage cavity was apparently never involved.

Without dwelling further on the special wound features of this infection, which will best be shown in the accompanying illustrations, I will briefly report the clinical features of the two cases; which in history, sequence of events, and wound appearances, seemed identical.

CASE I. H. B. T., age thirty-two, an apparently robust and healthy man of good habits, and without evidence of chronic infectious or degenerative disease; while on a visit to New York, experienced a sudden attack of acute abdominal pain associated with all the characteristic symptoms and signs of an acute fulminating appendicitis. As he was alone in a hotel he did not obtain expert advice for two days. At the time the writer first saw him in consultation with Doctor Mitchell, he had a temperature of 103, pulse 90. The abdomen was moderately distended and tender in all four quadrants; the area of maximum tenderness being at or near McBurney's point. Muscular rigidity was noted over the right rectus and neighboring muscles. As his prostration and general appearance seemed to indicate a grave infection, which had already existed for upwards of fifty hours, he was removed to the Roosevelt Hospital for immediate operation. On opening the abdomen, the appendix was found to be completely gangrenous, and surrounded by an abscess containing about 30 c.c. of thin foul-smelling pus. As the gangrenous process extended to the cæcum, after removal of the appendix, the cæcal opening was closed by a purse-string suture, and the point of closure reinforced by suturing a small appendix epiploica and a layer of omentum over the stump. A large cigarette drain was left *in situ*, and the peritoneum, muscles, and skin partly closed by layer suture. Although the anesthesia was satisfactory and the operation of short duration, the following day the temperature rose to 104, the pulse to 120; and the patient seemed gravely ill. There was, however, abundant drainage from the deep sinus necessitating frequent changes of the dressings.

On the third day, the cigarette drain was removed, and a rubber tube inserted, through which the wound was frequently irrigated and treated by the Carrel-Dakin method. The discharge from the deep cavity promptly diminished, soon ceased, and the sinus closed satisfactorily.

During this period the temperature gradually declined and the patient's condition improved; and at the end of a week, he seemed thoroughly convalescent and no further anxiety was entertained regarding his ultimate recovery.

On the seventh day after operation a peculiar deep purple œdema was noted around the points of entrance of the three upper silkworm gut sutures. These were removed, the cutaneous wound opened and packed with sterile gauze. Two or three days later to our surprise, the purple areas had not subsided, but apparently had extended to the margin of the then freely open cutaneous wound. They resembled six small carbuncles with beginning necrosis of the epithelial layer. Also it was noted that the edges of the wound beneath these lesions was undermined and presented isolated areas of white slough, which extended down to various levels in the subcutaneous fat. Incisions were later made into these areas of necrosis, and the entire wound packed loosely with gauze covering several Carrel-Dakin tubes, and was constantly treated with accurately prepared Dakin fluid. The original sloughs gradually separated, but beyond this loss of tissue,

there appeared an extending zone of the deep red edema, which formed an elliptical area of discolored skin about the size of a human hand.

As it was evident that the Carrel-Dakin treatment failed to control the process, a number of other antiseptic agents were tried including iodine, iodoform, various mercuric compounds, hot poultices, and finally exposure of the wound to X-rays, Alpine light, and the direct rays of the sun. None of these seemed to have the slightest effect on the slow progress of the disease, which gradually extended peripherally and sloughed centrally, until there was an ulceration which extended from a point near the iliac crest, to a point half-way to the lower costal border, and well over toward the median line, making an oval sloughing ulcer about 15 to 16 cm. in length by 10 or 12 cm. in width.

During the three weeks which had elapsed since the operation, the abdominal sinus had closed, the patient was practically afebrile, had a fair appetite, and seemed constantly improving. The only major complaint being, the intense pain which was occasioned by the dressings and any manipulation of the wound.

During the latter part of this period he was seen by perhaps six or eight members of the staff, including general surgeons, experts in dermatology, bacteriology, and internal medicine; none of whom had ever seen a similar lesion arising from an operative wound.

Numerous cultures were made from the tissues and wound secretions, as well as blood tests, to exclude syphilis, tuberculosis, blastomycosis, and other rare forms of infection. The wound cultures contained a large variety of organisms, but led to no definite conclusions.

At last, as it seemed evident that unless something far more radical were done in the way of treatment, a large part of the integument of the abdominal wall would be destroyed, it was decided to give a general anæsthetic and to circumscribe the entire diseased area, well beyond the lesion by an incision through the skin and entire thickness of the subcutaneous fat to the sheath of the rectus and aponeurosis of the external oblique muscles. This was done, and the long elliptical incision packed with gauze wet with a 1 per cent. solution of formalin. This was changed every day at first under gas anæsthesia, and the packing kept constantly wet with the same solution.

The sloughing process continued from the original edges of the ulcer toward the incision, but never passed this barrier; and when all the intervening tissues were destroyed, we had an extensive granulating surface with healthy edges, which quickly took on the normal process of repair. We hesitated to advise a skin graft on account of the doubtful nature of the process, and a very definite fear on the part of all who had observed its ruthless progress, lest any such procedure might again favor its reappearance.

By simple dressings and sun exposures, cicatrization took place rapidly, and at the end of thirteen weeks, the patient was discharged cured.

Shortly after the experience just related, there appeared in *Surgery, Gynecology and Obstetrics*, the report of a similar case by Dr. Thomas S. Cullen of Baltimore, admirably illustrated by two colored plates of the lesion. From Doctor Cullen's description of the etiology, symptoms, progress and wound appearances, I was convinced that our two cases represented examples of a rare but definite type of wound infection, probably due to some organism derived from the intestinal canal, as both arose from the operative treatment of a perforated intestinal lesion.

CASE II.—L. M., male, sixty-four years of age, although his appearance and athletic vigor would give one the impression of a much younger man. December 18, 1925, he was admitted to the Presbyterian Hospital for operation for acute appendicitis. The duration of his illness had been about thirty hours. On admission his temperature was 100.8, pulse 110; abdomen moderately distended with marked tenderness and muscular rigidity over the appendix area.

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OPERATION. The appendix was found to be partly gangrenous, perforated and surrounded by a collection of thin serous exudate. The intestines in the immediate neighborhood were reddened and covered with fibrin. The appendix was removed, the wound partly closed, and a large sigmoidostomy introduced which extended to the region of the appendix stump. He reacted favorably from the operation, the abdominal symptoms subsided, the temperature and pulse improved; and his general condition at the end of three days seemed entirely satisfactory.

On the fourth day small areas of necrosis were observed around the points of entrance



Fig. 1. Gangrenous infection of the wound. On the fourth day the lower granulating portion of the incision being drawn together by adhesive plaster.

of the wound from the abdominal gut entrance. The clitches were removed, the wound edges separated, and the wound lightly packed with gauze. The Carrel-Dakin method was employed, which at first seemed to act favorably, as for four or five days the wound showed no further changes. It did not then occur to the writer, that we had to do with other than a trivial secondary infection of the superficial wound. The deep drain was removed on the sixth day, and a small rubber tube substituted, and the deep wound frequently irrigated. About the tenth day, after the deep drainage sinus had ceased discharging, and the lower part of the wound seemed normally granulating, the same deep red discoloration and edema, as in Case I, appeared around the upper part of the

wound with four or five oval elevated lesions at the sites of the stitch openings. There was also noted a subcutaneous area of white slough, which extended from the edges of the wound upward beneath the unbroken but oedematous skin, toward the stitch openings. A day or two later, two or three of these necrotic areas were removed, leaving an irregular undermined unhealthy looking skin border. At this time also, it was noted that the deep purple oedematous nodules showed signs of breaking down, and that the area of hyperæmia was extending outward into the surrounding skin. One or two black areas were also seen along the skin margins. It was then recognized for the first time, that we had to do with the same type of spreading gangrenous cellulitis and dermatitis as in the first case.

January 9, under gas oxygen anæsthesia, the entire cutaneous margin of the wound was excised, including all of the reddened and oedematous tissues, the wound treated with peroxide of hydrogen, douched with sterile water, and packed with gauze soaked in and kept moist with Dakin solution. The process seemed arrested for two or three days; but later the same characteristic deep purple lesions occurred along the cutaneous borders, and sloughing of the fatty tissue was apparent. Both the red oedema and the subcutaneous necrosis spread more rapidly than at first, in spite of the most careful Carrel-Dakin technic; and the patient showed a definite increase in temperature and pulse rate. (Plate A.)

We were then convinced that the first excision had not been sufficiently wide to insure removal of the deeply imbedded organisms, which evidently had penetrated into the tissues well beyond the outermost limits of the hyperæmia and oedema. Again under gas-oxygen anæsthesia on January 18, a wider excision was made from 3 to 4 cm. from the wound edge. This time removing the entire wound and surrounding skin. The floor of the large wound thus created was treated by peroxide of hydrogen, douched with



FIG. 1. -The excised lesion.

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with saline, and packed with one per cent wet formalin gauze as in the first case. This treatment was given for two days, and constantly wet with the dilute formalin solution. The formalin was then discontinued and the regular Carrel-Dakin treatment carried out. This served to arrest the process, no further characteristic lesions appeared on the skin edges, and the entire wound took on a healthy granulating appearance.

The patient was discharged from the hospital at the end of seven weeks, and later at his home continued treatment by exposure to the sun, and the use of other stimulating measures. Dating from the last operation, the time required for the healing of this extensive wound was about eleven weeks. It occurred without the aid of skin grafts.

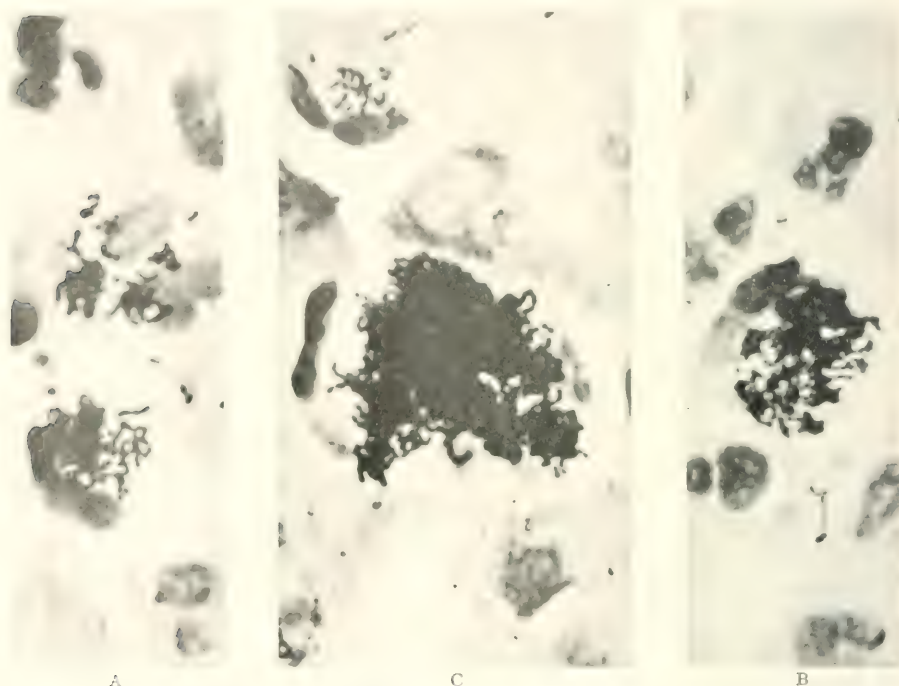


FIG. 2.—A. Phagocytes containing a few chains of cocci. B. A phagocyte distended with organisms. C. Tangled chains of organisms with cellular fragments in the neighborhood. Gram stain. Oil immersion lens.

As in my first case, the one most distressing symptom was the acute sensitiveness of the wound, making dressings and all manipulations about the lesion extremely painful.

It is worthy of note also that as soon as the specific infection was killed, this sensitiveness promptly disappeared.

Since the observation of my second case, four other similar cases have been brought to my attention.

THE first of these was a woman, thirty-three years of age, who was admitted to the Presbyterian Hospital in January, 1919, for observation. Four or five months before her admission, what was thought to be a cold abscess was present in the upper right quadrant of the abdomen. This was opened and drained. Shortly after the operation, there occurred a slowly spreading gangrenous ulceration of the skin, beginning at the wound edges, and extending in all directions, until, at the time of her admission to the hospital, the ulcerated area occupied a large part of the upper half of the abdomen, and extending well down into the right flank.

The process had been exceedingly slow, and at first was thought to be due to syphilis, tuberculosis, or one of the mycotic infections. Each of these, however, was excluded by careful tissue examinations, bacterial cultures, and inoculation experiments. The cultures from the tissues and wound secretions showed a large variety of organisms, but no definite conclusion was reached. Although the origin of the original abscess, whether mural, or intra-abdominal and possibly due to a small perforative lesion, could not be ascertained. Doctor Whipple, who saw the case several times in consultation, informed me that it was similar in many respects to my second case.

The second was one reported at the joint meeting of the New York and the Philadelphia Surgical Societies during the past winter by Dr. F. G. Alexander. His case also followed operation on an acute perforative appendicitis. The progress of the case was similar to the two reported in this paper, and although he strongly advised complete excision of the area, the patient refused operative treatment, with the result that the ulceration continued to extend until it involved a large part of the right half of the abdominal wall, the right buttock and thigh to the knee. His patient was in the hospital eleven months. The other two cases were, one reported by Dr. Christopher, of Chicago, and another which occurred in the service of Dr. A. V. Moschowitz, of New York.



FIG. 1. Ulceration of the abdominal wall.

As soon as I recognized that the process in my second case was the same as in my first patient, I called in consultation Dr. Frank Lamont Meloney of the Surgical Staff of the Presbyterian Hospital,

who is particularly interested in surgical infections, with a view to obtaining his advice and coöperation in determining the causative organism or organisms. He observed the patient from time to time, and entered enthusiastically into the plan of establishing the bacteriology of the process. The report of his observations and inoculation experiments is as follows.

Bacteriological and Experimental studies. The fluid from the purulent abscess was cultured in the usual way by a member of the laboratory staff. A pure culture of non-hæmolytic streptococcus was reported. No anaërobic cultures were made and it is not on record whether or not the culture grew in the usual manner on the surface of a blood agar plate. It therefore remains an open question whether this organism was or was not the same streptococcus which is to be described below. Later, when the gangrene developed in the wound, a second routine aerobic culture revealed a hæmolytic staphylococcus aureus and a diphtheroid bacillus. The streptococcus was not found.

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Subsequently a special study was made of the slough from the wound. A hemolytic streptococcus, *Streptococcus pyogenes*, and a diplococcal bacillus were found again aerobically, while the anaerobic blood agar plates revealed a streptococcus which would not grow on the aerobic plates.

When the region was prepared for complete excision, the surface was painted copiously with iodine in order to minimize surface contamination. A culture was taken



Fig. 1. The ulcer on the neck of the patient, showing the area of the ulcer and the area of the incision. The ulcer is a large, dark, and possibly necrotic area in the center of the neck. The incision is a line of small, dark, and possibly necrotic areas on the neck.

of the blood drawn by the first incision (at point 1 in Fig. 1). After excision, the complete specimen was taken in a sterile towel to the laboratory, the surface was again painted with iodine and incisions were made just beyond the gangrenous margins of the ulcer at points 2, 3, 4 and 5 in Fig. 1. Direct smears of the tissue fluid in these regions showed, in the two nearest the margin, great numbers of very small cocci growing in masses of tangled chains. Many of these were found to be contained in leukocytes (Fig. 2a), some stretching the cell membrane almost to the bursting point (Fig. 2b), and others in masses much larger than the phagocytes with cellular debris in the neighborhood (Fig. 2c). These findings seemed to represent different stages in the battle between the foreign invaders and the host, with apparent demonstration that the organisms were not only growing in the tissues, but in the phagocytes as well. In the two regions farther from the margins, diplococci and short chains were found both within and without the tissue cells and wandering cells. Sections of the tissue stained for

bacteria revealed them in great numbers (Fig. 3). Cultures were made from the five points mentioned above, aerobically and anaerobically on five per cent. sheep blood agar plates and in cooked meat medium with and without dextrose. In twenty-four hours three out of four of the cultures yielded, in pure culture, a non-hemolytic streptococcus which grew in the cooked meat medium with or without dextrose, both aerobically and anaerobically. On the blood agar plates, however, it failed to grow except under anaerobic conditions, the aerobic plates being without any evidence of growth. The fourth culture showed beside the streptococcus a few colonies of non-hemolytic staphylo-

coccus albus on the anaërobic plate, possibly an air contamination. After forty-eight hours the culture of the blood from the incision revealed a pure culture of the same streptococcus. Thus in four out of five cultures from regions extending from just outside the margin of the ulcer to the limits of excision, this organism was found in pure culture, evidently growing in the tissues and successfully combating the defensive efforts of the host. The evidence seemed to be strong that this bacterium was in some way related to the disease process. Contrary to expectation, the hæmolytic staphylococcus aureus and the diphtheroid bacillus cultured from the slough, were not found in the zone outside of the gangrenous margin. This we considered to be most significant because it indicated that for the infection as a whole the streptococcus was the more important. Experiments were then carried out in order to determine the cultural characteristics and the pathogenicity for animals of this streptococcus.

Cultural Characteristics.—

It is a very small coccus growing in chains of varying lengths. The individuals are approximately 0.2–0.5 microns in diameter. It is Gram-positive. It grows readily in the anaërobic jar in cooked meat medium with two-tenths per cent. dextrose. In this medium it tends to form tangled chains in a manner similar to its growth in the tissues. It develops much less readily aerobically in the cooked meat medium with dextrose. Anaërobically on five per cent. sheep blood agar plates in twenty-four hours it grows with small pin point non-hæmolytic colonies which become slightly green on standing in the air. (As already mentioned some of the blood agar plates until it had been passed through nine aerobic subcultures in cooked meat medium. It then very slowly developed minute colonies. This ninth subculture was sealed and kept for a month in the ice box. It was then found to have lost its ability to grow aerobically on the blood plates.) When grown anaerobically this organism will ferment dextrose, lactose, saccharose and salacin, but not mannite. It is killed in fifteen minutes when heated to 60° C. The organism may, therefore, be classified as a non-hæmolytic micro-aërophilic streptococcus, similar in many respects to certain of the intestinal streptococci. The intestinal origin of the streptococcus in this case is not proven; it is only presumptive.



FIG. 1. The ulcer slightly reduced.

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Animal Experiment. Two cubic centimetres of a twenty hour culture in cooked meat medium with 0.005 per cent dextrose injected into the peritoneum of a mouse failed to kill. Two cubic centimetres in the peritoneum of a guinea pig failed to make the pig ill, but the organism was recovered from the peritoneum after two weeks and, in another instance, a month later. When the ninth subculture mentioned above had acquired the faculty of growing on aerobic plates, it was injected into the peritoneum of a guinea-pig. It was recovered after twenty-four hours and was then found to have lost the faculty for aerobic growth. Five cubic centimetres subcutaneously in guinea-pigs and rabbits produced slight redness and swelling which appeared on the day after injection, but rapidly subsided. There was never any evidence of gangrene. These



Fig. 7. Guinea pig, 11 days after the injection, showing undermining. Life size. Slightly reduced.

failures to demonstrate pathogenicity for animals seemed to controvert the very definite evidence of activity in the tissue of the patient. It was then suggested to try the effect of this organism combined with the hæmolytic staphylococcus aureus and the diphtheroid bacillus with which it was found associated in the actual gangrenous margin of the wound. Two cubic centimetres of a twenty hour culture of each organism were injected subcutaneously into control guinea-pigs and into another pig one cubic centimetre of the hæmolytic staphylococcus aureus was combined with the same quantity of the non-hæmolytic micro-aërophilic streptococcus. In still another pig the streptococcus

was combined with the diphtheroid bacillus. In twenty-four hours the staphylococcus combined with the streptococcus had produced a large, red, tender swelling two by three centimetres in diameter with a central area of discoloration indicating beginning gangrene. The staphylococcus alone produced a somewhat smaller, red, tender swelling, without any evidence of gangrene. The streptococcus alone produced only a slight red swelling, as did the combination of streptococcus and diphtheroid bacillus. The diphtheroid bacillus alone produced no lesion.

In the second twenty-four hours the lesion with the staphylococcus alone increased slightly in size but thereafter subsided, finally localizing as a small abscess from which the organism was recovered after two weeks. The lesion produced by the combination of staphylococcus and streptococcus increased in the second twenty-four hours and a large irregular area of frank gangrene developed which separated at the margin after five days and sloughed out. Both organisms were recovered from the lesion. This experiment was repeated twelve times in guinea-pigs and rabbits and in every case but one produced a large lesion with more or less gangrene. The lesion in one of the guinea-pigs is shown in Figs. 7 and 8. In one rabbit the mixture produced no gangrene but an abscess formed three times the size of the controls. In one instance a silkworm gut suture contaminated with the staphylococcus was passed through an area into which the streptococcus had been injected, and it was tied with moderate tension. Gangrene

developed around the suture with a wide zone of swelling outside of it. The process generally reached its peak in three to four days, and thereafter subsided. It did not spread progressively as in the human case. On three occasions out of nine the staphylococcus, when injected alone twice in a double dose and once in a single dose in small pigs, produced some superficial gangrene, but in six cases it simply formed a small abscess. Because of this occasional inconsistency, the experiment was repeated in a dog in order to use an animal with thicker skin and more subcutaneous tissue. On the right side the staphylococcus was injected alone, on the left side the streptococcus alone and in the centre the same quantity of these two, mixed together. A total volume of five cubic centimetres was injected into each area, the pure cultures being diluted with broth. Care was taken to put each injection into the subcutaneous tissue with a minimum of trauma at the point of injection. In twenty-four hours a moderate swelling appeared at the site of the staphylococcus injection and a slightly larger one at the site of the combination. Only slight swelling appeared where the streptococcus was injected alone. In four days the mixture had produced a large swelling four times as large as the staphylococcus alone and there was an irregular patch of early gangrene in the centre. The staphylococcus lesion thereafter subsided without gangrene.



FIG. 1.—The lesion produced by a mixture of streptococcus and staphylococcus. The swelling at the centre of the lesion is reduced.

On the fifth day frank gangrene developed at the injection site of the mixture and on the sixth day it sloughed out, leaving an undermined gangrenous margin. This spread slightly for a day or two and then subsided, but showed very little tendency to heal. The dog died of pneumonia on the eighteenth day after inoculation. Stages of this process are shown in Figs. 4, 5, and 6. The similarity of Figs. 1, 6, and 8 is striking.

Comment.—Although no definite conclusions can be drawn from these experiments, there seems to be evidence that in guinea-pigs and in rabbits and in the only dog in which the experiment was tried the non-hæmolytic micro-aerophilic streptococcus and the hæmolytic staphylococcus aureus cultured

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specimen patient's wound, when injected together produced gangrene almost invariably, while these organisms injected separately did not—the streptococcus never and the staphylococcus only rarely in small guinea pigs. These experiments suggest that a certain symbiotic function or a combination of functions of these two organisms may be necessary for the production of the gangrene. The rarity of its occurrence clinically may be explained by the



FIG. 1. A patient with progressive gangrenous infection of the skin.

necessity for the coincidence of two such organisms in the wound. The streptococcus is much more rare in its occurrence than the staphylococcus aureus and might easily be overlooked in routine cultures.

Which organism is the essential one in the production of gangrene is a question not yet fully answered. In this patient the streptococcus was found more extensively invading the tissues while the staphylococcus was only present in the gangrenous margin. When the gangrenous margin was partially excised, the process continued to spread, but when it was completely removed, the process ceased. Even though the cut margin yielded a growth of the streptococcus, the body took care of the infection which remained. In animals the staphylococcus

produced the greater lesion when injected alone, but on one occasion a mixture of the streptococcus with a control hemolytic staphylococcus aureus produced an extensive gangrenous lesion, while the staphylococcus from this case mixed with the diphtheroid bacillus produced no gangrene. We favor the following explanation for the phenomenon. *The infection with streptococcus prepared the way for gangrenous process, but for its actual production a second organism was necessary—in this case the staphylococcus aureus.*

The solution of this problem will require more extensive experimentation. The reaction of laboratory animals to infection is often so different from that of human beings that it is important to take every opportunity to study this condition as it exists in man. These cases are so uncommon that it is not likely that one person would have the opportunity to study such a condition more than once or twice. Our findings are reported in detail in order that they may be compared with similar studies made by other observers. It will be of interest to search for such a combination of organisms in other lesions of this kind for it is only by repeatedly finding these conditions prevailing, that we can be certain that the cause of the disease has been demonstrated. It is not unlikely that such combinations were present in the cases previously reported by Cullen of Baltimore, Christopher of Chicago, Alexander of Philadelphia, in the case observed by Moschcowitz of New York and in the first case seen by Doctor Brewer.

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GASTRIC MOTILITY

I. THE ORIGIN AND CHARACTER OF GASTRIC PERISTALSIS*

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METHODS

The original purpose of this study was to ascertain the effects of the various surgical procedures on the character of gastric peristalsis and the motility of the stomach. Various possible methods of study presented themselves:

First, observation of the stomach by means of the roentgen ray following the operation, and comparison with the normal.

Second, the insertion of a balloon into the stomach and the study of the gastric waves as transmitted by the balloon and recorded on a smoked drum after the various operations.

Third, observation of the stomach in situ through a laparotomy incision after surgical operation at an earlier date, and

Fourth, excision of the stomach in toto and suspension in a warm bath of Ringer's solution.

The third method was selected because it furnished direct visual evidence of the phenomena that were taking place, and because it afforded more normal conditions than the last method. It was also planned to make concurrent studies with the roentgen rays.

After some of the early experiments it became evident that the motor phenomena of the stomach under the conditions of these experiments did not entirely agree with the conception of them held by many physiologists. It was therefore decided to confine this work to the study of normal gastric peristalsis and the pylorus. These experiments were completed in 1922, but owing to illness could not be reported sooner.

It is known that a laparotomy usually causes a cessation of peristaltic activity due to the reflex inhibitory impulses that are set up. To overcome that difficulty, Auer¹ suggested sectioning one or both groups of extrinsic nerves. Because of the ease with which vagus section may be performed, that procedure was decided on for this work. The objections that may be raised against the method will be considered presently.

Only dogs were used in the experiments. At first the vagi were sectioned in the neck. Nearly all these animals died of broncho-

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1. Auer, J.: The Course of the Contraction Wave in the Stomach of the Rabbit, *Am. J. Physiol.* **23**:165, 1908-1909.

pneumonia, probably following the paralysis of the laryngeal muscles. One of these animals was alive two weeks after the date of sectioning, but was vomiting nearly all the food he ate, owing to a paralysis of the esophageal muscles. For these reasons vagus section in the neck was abandoned and the nerves were divided just as they emerged through the diaphragm.

The nerves are easily reached through a high midline incision. If the lesser curvature is put on the stretch, they are felt as two firm, unyielding cords on either side of the curvature. The section was performed as high up as possible in order to reach a point above that at which the branches are given off. Even so, later necropsies occasionally showed that a branch was given off in the chest and that this branch, passing down independently of the main trunks, had not been severed. As this work was not concerned with the effects of vagus section but rather with motility, such an occasional finding did not vitiate the results. Postmortem examination was always performed and among other things the vagus section was noted.

As some authors have reported ulcers following vagus section, I incidentally state that there was not the slightest indication of a lesion comparable to an indurated ulcer in any of the animals.

Twenty-five healthy animals were examined after vagus section. In two of these, bilateral section had been performed in the neck; in two, unilateral section had been carried out in the abdomen, and in the remainder, both vagi had been severed at the level of the diaphragm. The operation had been performed in a much larger number, but the remainder developed distemper during several epidemics in the laboratory and were therefore discarded. In addition, sleeve resection was performed on two animals; a V resection of the reentrant angle on four, and an excision of a small area of the anterior gastric wall on two. In all the latter, bilateral vagus section also was done.

A transverse upper abdominal incision under light ether anesthesia was usually made one week after vagus section. The stomach was left in its natural surroundings. All exposed surfaces were kept moist by the continuous drip of physiologic sodium chlorid solution at body temperature.

It is difficult in the extreme to study organs experimentally and yet retain normal conditions. Nevertheless, even though the anatomy of an organ, for instance, is altered, it does not necessarily follow that all the experimental results obtained under such conditions are inapplicable to the normal organ. A dog equipped with a "Pawlow stomach" and a gastric fistula can hardly be said to possess a normal organ. Yet the phenomenon of the appetite juice, which among others was firmly established by this experimental procedure, is by general consent held to be just as true for the intact stomach. Also, if one group of

findings is confirmed by a second experimental procedure that is entirely different from the first, that confirmation lends added importance.

In this work an attempt was made to see the stomach while it was at work. The factors that had to be overcome were the inhibitions to the gastric motor phenomena due, first, to reflexes from the incised abdominal wall, and, second, to the emotions that would be aroused in the dog were he to feel and see the experimental procedures. To overcome the first difficulty, the vagi were incised, as has already been stated; to overcome the second, a light ether anesthesia just sufficient to abolish consciousness was used. Do the cut vagi, the ether anesthesia, and the exposure of the organs following the laparotomy render the results obtained inapplicable to normal conditions?

Our knowledge concerning the extrinsic nerves of the stomach is as yet incomplete, but one fact seems certain. We cannot regard the vagi as purely motor, and the splanchnics as purely inhibitory; both systems of nerves carry motor and inhibitory fibers. Thomas and Wheelon,² who give an excellent summary of the experimental investigations on the gastric extrinsic nerves, conclude from their own work that stimulation of the vagus leads to motor responses in about 90 per cent. of the trials, and to inhibitory responses on the pyloric sphincter in 10 per cent. In the case of the splanchnic nerves, stimulation leads to motor responses in 63 per cent. of the trials and to inhibitory responses in 37 per cent. In other words, under the conditions of their experiments motor phenomena were far more frequent following the stimulation of either system, and their work bore out the findings of others that the vagi did possess inhibitory fibers.³

What is more striking is the fact agreed to by many that the stomach may function with apparently little or no change following the division of either or both of the extrinsic systems of nerves. Thus Cannon⁴ found that after severing the vagi in cats there was a temporary slowing of the gastric peristalsis and a lowering of tone, but that the animals recovered from these effects within a few days. Auer⁵ found

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in rabbits that a few days after section of the vagi or splanchnics, or both, the peristalsis is once more normal in rate, rhythm and strength. Borchers,⁶ who observed the peristalsis in cats through a window in the abdominal wall, found that five days after vagus section the peristalsis was once more normal. Aldehoff and Von Mering⁷ and Kirschner and Mangold⁸ reached a similar conclusion, and May⁹ reports vagotomy performed without lasting effect in rabbits, dogs, cats and apes.

In the majority of the experiments performed by me, the peristalsis was studied from seven to ten days after the section of the vagi. Peristalsis was present in spite of the abdominal incision in about three fourths of the dogs. It would seem that in these dogs the section of the vagi had removed a sufficient number of inhibitory fibers to permit the persistence of peristalsis even after laparotomy. Furthermore, the interval mentioned above was found to be the best. If a much longer period was permitted to elapse after vagus section, peristalsis was only very rarely seen after laparotomy. Perhaps that was due to the establishment of a compensatory action by the remaining inhibitory fibers of the splanchnics. However, as all these observations were made at a time when, according to all the authorities mentioned above, normal peristaltic relations had once more been established after the vagotomy, it appears to be fair to regard the motor phenomena that were found as closely similar to, if not the same as, those occurring under normal conditions.

Does the administration of a light ether anesthesia render the results inapplicable to normal conditions? The abdominal wall of the rabbit is quite thin, and if the abdominal hair is shaved the peristaltic waves may be seen to course down the stomach after a full meal. Auer,¹⁰ utilizing that fact, made careful observations of this peristalsis. Certainly this method comes very close to nearly normal conditions. Besides watching the course of the peristaltic waves, he made graphic records of them by placing a Marey receiving tambour on the pyloric third of the stomach. In addition to other work, the effect of the administration of an ether anesthetic was studied. With the exception of some irregularity at first, due to inhibitions set up from the nasopharynx

Aldehoff and Von Mering: Anteil des Nervus Vagus an der motorischen Innervation des Magens im Hinblick auf die operative Therapie von Magenkrankheiten, Studien zur Physiologie und Pathologie der Magen Chirurgie, Beitr. z. klin. Chir. **122**: 547, 1921.

7. Aldehoff and Von Mering: Ueber den Einfluss des Nervensystemes auf die Funktion des Magens, Verhandl. d. Cong. f. inn. Med. **17**:333, 1899.

8. Kirschner and Mangold: Die motorische Funktion des Sphincter Pylori und des Antrum Pylori beim Hunde nach der queren Durchtrennung des Magens, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:446, 1911.

9. May (Footnote 3, third reference).

10. Auer (Footnotes 1 and 5).

during induction, he found that gastric peristalsis is "at least as regular as before the anesthesia. This regularity is maintained even when the corneal reflex is absent." Apparently, then, light ether anesthesia does not have any profound effect on gastric peristalsis. Certainly there is no evidence that it helps to create irregular types of waves. And the evidence presently to be advanced lends added support to these findings. Wheelon and Thomas¹¹ also found an ether anesthesia entirely satisfactory for their studies on the effects of stimulation of the extrinsic nerves.

Except when otherwise stated, the dogs were fed one-half hour before the observations. The meal totaled 400 c.c. In some of the later experiments different quantities were used and this is so stated. The meal consisted either of broth with meat and bones or of milk with or without bread.

Following the laparotomy for the study of the gastric peristalsis in the dogs, the exposed surfaces were kept continuously moist and warm with physiologic sodium chlorid solution. The edges of the wound were not widely retracted, but were held open only sufficiently to permit observation of the parts desired. Several dogs were studied while entirely immersed in a warm bath of physiologic sodium chlorid solution, but as this method did not seem to afford any added advantages, the former method was resorted to. The results reported are not at variance with findings obtained by other methods.

The discussion has been divided into the following parts:

- I. The origin of the gastric wave.
- II. The character of the gastric peristaltic wave.
- III. The conduction of the gastric peristaltic wave.
- IV. The relation of the antral contraction to the discharge of food-stuffs through the pylorus.
- V. The mechanism of the pylorus; and under this a discussion of (a) the chemical theory of control; (b) the mechanical theory of control, and (c) the probable manner of pyloric control.

Divisions I and II form the subject of the present article; Division III will be taken up in a second article, and Divisions IV and V in a third.

RELATION OF THE GASTRIC WAVES

During recent years there has been a tendency to ascribe to the stomach physiologic phenomena parallel to those found in the heart. And such an attempt can be readily understood, for it would help much to clarify some of our conceptions of the physiology and surgery of

11. Wheelon, H., and Thomas, J. E.: Observations on the Motility of the Antrum and the Relation of the Pyloric Sphincter to That of the Antrum. *J. Lab. & Clin. Med.* 6:124 (Dec.) 1920.

the stomach were we able to show the presence of a nodal center in which the gastric waves arise and a conduction system through which they are propagated.

It has been accepted for the most part as true that the gastric waves commence in the body of the stomach. Hoffmeister and Schütz,¹² in their classical experiments, described them as commencing on the greater curvature at a level a few centimeters below the cardia. Their experiments, which will be fully detailed below, were performed on the excised stomachs of dogs. Much later, Cannon¹³ found that the first waves were usually seen in the pyloric region, and that following waves began nearer to the cardia. He believed that there was no special site for the origin of the waves, but that they originated in a "tonus ring" (a contracted ring of the circular musculature) when the latter was distended by an increase of the internal pressure, and that the contraction thus started was propagated in a downward direction. He could not state, however, what the conditions were for the establishment of these "tonus rings."

But now an attempt has been made to find a gastric pacemaker that would correspond in some degree to the sino-auricular node of the heart, and it seems possible that such a center exists on the lesser curvature at the cardia, close to its junction with the esophagus. The evidence in favor of such a view is both anatomic and experimental.

While working on the nerve structures in the stomach of the rabbit, Openchowski¹⁴ found eleven groups of ganglions on the lesser curvature at the cardia. These lay on the serosa and were in close relation to the fibers of the vagus and the sympathetic. More recently Keith,¹⁵ while studying the nature and origin of the nodal and conducting tissue of the heart, turned his attention to the alimentary tract in the hope that he might there discover a similar structure in a less highly developed state. He found in his examinations of the stomachs of a large number of mammals that the myenteric plexus was well developed both in the pyloric division of the stomach and along the lesser curvature, but that it was much less abundant elsewhere in the gastric wall. Further, at the ring just distal to where the esophagus ends, there was a distinct modification of the musculature and of the plexus. Here he found a definite development of neuromuscular junctional tissue—"just such an area or node—etc. for a nodal center of the stomach." In the porcupine,

12. Hoffmeister and Schütz: Ueber die automatischen Bewegungen des Magens, *Arch. f. exper. Path. u. Pharmakol.* **20**:1, 1885.

13. Cannon, W. B.: *The Mechanical Factors of Digestion*, New York, 1911, p. 189.

14. Openchowski: Ueber die nervösen Vorrichtungen des Magens, *Zentralbl. f. Physiol.* **3**:1, 1889-1890.

15. Keith, Arthur: A New Theory for the Causation of Enterostasis, *Lancet* **2**:371, 1915.

the microscopic appearance of the tissue at this junction was very similar to that of the sino-auricular node in the heart of this animal. Keith concluded from his studies that a main nodal center for the stomach existed at the cardia and that in it the rhythmic contractions of the stomach were initiated.

The fine work of Alvarez¹⁶ has added strength to this conception in recent years. Working first with muscle strips excised from different portions of the stomach, he showed that those excised from the lesser curvature near the cardia possessed a greater tendency to rhythmic contraction than those from any other part of the stomach, and that only the former strips could be counted on to give typical and regular contractions in every case. The rate of rhythmic contraction was most rapid at the cardia, a little slower on the lesser curvature down to the angle, and much slower in all other parts of the stomach, especially in the antrum. He further showed that with electrical stimulation of the different portions of the stomach wall the lesser curvature near the cardia displayed the shortest latent period; the rest of the lesser curvature was next, then the greater curvature, and finally the antrum. The tests for irritability yielded similar results, because stimuli that were too weak to cause a contraction in other parts of the stomach nevertheless produced that effect on the muscle from the cardia. Barbera¹⁷ long ago reported like findings; when applying a weak faradic current to the stomach of a frog, he found that the first contraction always appeared at the cardia, entirely regardless of whether the stimulus was applied there or to the fundus or to the antrum, and that this contraction was then followed by a typical peristaltic wave.

Since, then, there is an accumulation of tissue on the lesser curvature at the cardia which closely resembles a nodal center, and since the muscle here possesses a higher degree of irritability, rhythmicity and contractility than any other portion of the gastric wall, it seems fair to assume that this part of the stomach acts as a gastric pacemaker.

But if this is true, why do not the gastric waves commence at that point? The roentgen ray apparently shows them to start, as Cannon¹⁸ first pointed out, in the body of the stomach. But it does not necessarily follow that their actual point of origin is at the level at which they first appear on the fluoroscopic screen. For it is surely possible that a

16. Alvarez, W. C.: Differences in Rhythmicity and Tone in Different Parts of the Wall of the Stomach, *Am. J. Physiol.* **40**:585 (June) 1916; Differences in Irritability and Latent Period in Different Parts of the Wall of the Stomach, *Am. J. Physiol.* **41**:320 (Sept.) 1916; *The Mechanics of the Digestive Tract*, New York, 1922.

17. Barbera: Ueber die Reizbarkeit des Froschmagens, *Ztschr. f. Biol.* **26**: 239, 1898.

18. Cannon (Footnote 13, p. 48).

very shallow contraction of the gastric muscle may not cause a sufficiently deep indentation in the shadow cast by the barium meal to make it readily perceptible.

In the dogs examined at the laboratory, it seemed evident that the gastric waves commenced in nearly all cases at the level of the cardia. High up in the body of the stomach there usually was no indentation. But what Alvarez has very aptly called a "ripple" was readily discernible, and as this ripple spread downward it gradually grew deeper and formed the peristaltic wave visible by the fluoroscope.

That, too, seems to be the conclusion of Auer¹ and of Alvarez,¹⁹ who is applying the galvanometer to a study of the contractions of the stomach. The electrical records show that "many of the waves which seem to begin in the lower third of the stomach have come as shallow ripples from a pacemaking region near the cardia," and that definite electrical disturbances are traveling down the upper part of the stomach in advance of the peristaltic wave, even when no movement of the muscle can be detected.

CHARACTER OF GASTRIC PERISTALSIS

Today our conceptions of the gastric peristaltic wave are for the most part dependent on the shadows seen on the fluoroscopic screen. And this picture is so readily available that the possibility of the waves being quite different under other conditions is hardly considered. But it seems quite certain that other types do occur.

As previously stated, the roentgen ray shows the wave commencing about the middle of the stomach. Shallow at the onset, it slowly deepens till it reaches the antrum, but from here on it increases markedly in depth and intensity until it reaches the pylorus. In addition, Cole²⁰ has described a further phenomenon, to which Alvarez,¹⁹ after his electrical studies, also subscribes. While the waves are progressing downward, and several may be present in the stomach at one time, there is a rhythmic increase and diminution of the gastric tone, resulting in a constriction and dilatation of the gastric lumen, and of the waves that are then present. Cole terms the former systole, and the latter diastole.

The first discordant voice of recent times was raised by Auer. His description is closely reminiscent of the work of the earlier physiologists. Stated very briefly, these pioneers believed that after the wave reached the antrum the musculature of the latter contracted as a whole, much

19. Alvarez, W. C.: New Light on Gastric Peristalsis, *Am. J. Roentgenol.* **10**:31 (Jan.) 1923; Action Currents in Stomach and Intestine, *Am. J. Physiol.* **58**:476, 1921-1922.

20. Cole, L. G.: The Physiology of the Pylorus, Pilleus Ventriculi and Duodenum as Observed Roentgenographically, *J. A. M. A.* **61**:762 (Sept. 6) 1913; Motor Phenomena of the Stomach, Pylorus and Cap Observed Roentgenographically, *Am. J. Physiol.* **42**:618, 1916-1917.

like the ventricle of the heart. The newer view is that the normal peristaltic wave progresses uninterruptedly from its point of onset to the pylorus, passing over the antrum as a wave. It is very curious that all methods for the investigation of gastric motility, with the exception of the roentgen ray, yield results tending to show the existence of the former type of wave.

Beaumont,²¹ who, it will be remembered, observed the stomach in man through a gastric fistula, gives his findings in the following words:

"The longitudinal muscles of the whole stomach, with the assistance of the transverse ones of the splenic and central portions, carry the contents into the pyloric extremity. The circular or transverse muscles contract progressively, from left to right. When the impulse arrives at the transverse band, this is excited to a more forcible contraction, and closing upon the alimentary matter and fluids contained in the pylorus, prevents their regurgitation. The muscles of the pyloric end, now contracting upon the contents detained there, separate and expel some portion of the chyme."

This was written in 1833.

A half century later, Hoffmeister and Schütz¹² performed their work on the stomachs of dogs. The stomach was excised after the animal was bled to death; then it was suspended in a moist chamber by means of the lesser omentum. The movements were observed through a glass window. These workers divided the gastric cycle into two parts. During the first part, the peristaltic wave begins on the greater curvature, a few centimeters from the cardia, and then passes downward, growing gradually deeper until it reaches the "sphincter antri." The second phase begins with the contraction of the "sphincter antri," which at that point practically obliterates the lumen and divides the stomach into two parts. (The term "sphincter antri" is applied to the ring of circular muscle at the beginning of the antrum.) Then follows either a general contraction of the antral musculature, including the circular, the oblique and the longitudinal, or first a shortening of the length of the antrum by one-third or one-fourth, and then a contraction of the circular muscle. They never observed peristaltic transmission of the wave in the antrum. Relaxation did not occur generally, but started in the beginning of the antrum and extended down to the pylorus. To the entire cycle they gave the name peristole. Not all the cycles were of this typical type. The most common variation was for either the first phase or the second to occur without the other. Occasionally they saw a rapid wave start at the closed pylorus and run back to the sphincter antri, terminating with a contraction of the latter. These retrograde waves were seen only in those stomachs that contained coarse food; so they concluded that some coarse particles had gotten into the

21. Beaumont, William: *The Physiology of Digestion*, Burlington, 1847.

antrum and, not having been pushed through the pylorus by the preceding wave, were now being forced back into the body of the stomach.

Auer,¹⁰ utilizing the fact that the abdominal wall of the rabbit is very thin, and that if the hair is removed gastric peristalsis is easily visible through it, was able to watch the gastric peristalsis without opening the abdomen—certainly under very ideal conditions. The waves which he saw corresponded closely to those described by Hoffmeister and Schütz. Occasionally, however, a wave progressed uninterruptedly to the pylorus, just as it is seen to do on the fluoroscopic screen. Borchers,⁶ who inserted a glass window into the abdominal wall of the cat and in that manner studied the behavior of the gastric waves, also found them to be similar to those described above.

After studying the dog's stomach for some time I received more and more strongly the impression that there is no such thing as a single normal type of peristaltic wave. There are at least two main types, but variations within these are quite common. Let us consider first the type corresponding to that described by Beaumont, and as outlined above.

The wave starts on the body and the greater curvature on a level with the cardia. During the early part of digestion, it is very shallow but later becomes more marked. Progressing downward it grows deeper and deeper until it finally reaches the reentrant angle at the beginning of the antrum. Sometimes the lesser curvature participates in these waves, but for the most part they are limited to the lateral and great curvatures. This might be termed the ending of the first phase.

Then the following happens: The constriction at the level of the antrum (what has been called the sphincter antri pylorici) grows rapidly deeper without moving onward, that is, it remains at the same level. While this is occurring, there is at the same time a concentric contraction of the entire antrum in which both the circular and the longitudinal fibers participate, so that the antrum diminishes both in circumference and length. These contractions finally effect a total obliteration of the antral lumen. So firm are they that at their completion the antrum looks like a hard, white, bloodless cord, and feels almost as firm as bone. Its length, too, is considerably shorter than that of the relaxed antrum, a fact that should be borne in mind in roentgen-ray observations. One can often hear fluid being squeezed through the pylorus while the foregoing contraction is taking place. Relaxation does not occur generally throughout the antrum, but begins at the angle and spreads downward toward the pylorus so that the proximal portion of the antrum is quite relaxed when the most distal portion is just beginning to be so. This contraction of the antrum as a whole may be called the second phase.

There can be no doubt of the existence of such a type of wave. I have seen it hundreds of times when I was looking directly at the stomach. Others have seen it in the excised stomach, in the stomach *in situ* observed through a celluloid window, and through the thin abdominal wall of some animals. To dismiss it as a wave seen only under abnormal conditions cannot be done, for as has already been stated, Auer saw it through the intact abdominal wall of the rabbit, and Holzknacht²² has seen it with the roentgen ray in man. The fact that the wave later referred to is the one usually seen by means of the roentgen ray can mean only that that is the type of wave that occurs under the conditions that are used to elicit it.

Both in its first and second phases this wave presents several variations. The wave coursing down over the body may not progress as far as the angle, but may gradually grow shallower and disappear when only one-half or two-thirds of the way from its goal. Or it may pass all the way down to the angle and stop there without being followed by a contraction of the antrum.

But it is the variations of the second phase that are the most interesting. To begin with this phase may occur entirely independent of the first. Thus, without any warning there may be a contraction of the antral sphincter, followed by a contraction of the antrum as a whole. At other times the wave coming down from the body may continue almost to the center of the antrum before the latter begins its systolic contraction. There are times, too, when the antrum has contracted independently of a wave from above, and then while it is relaxing a wave coursing down the body reaches it. The antrum does not respond by another contraction but continues its relaxation. The whole phenomenon reminds one very much of an extrasystole of the heart with the resultant refractory stage of the ventricle.

The second type of wave need not be so minutely described, for it is the one usually seen with the roentgen ray. Commencing at the same level as the wave described above, it passes downward, growing gradually deeper, and progresses uninterruptedly to the pylorus. While it is passing through the antrum, a contraction of the longitudinal fibers occurs at the same time, so that the length of the antrum decreases and the contraction grows more marked the nearer the wave is to the pylorus. Often there is a systolic contraction of the distal centimeter or two. I have never seen this type of wave begin independently at the angle, although I see no reason why this may not occur. The rhythm of both types is the same, there usually being from three to four waves per minute.

22. Holzknacht, quoted from Kaestle, Rieder and Rosenthal: The Complex Motor Phenomena of Various Types of Unobstructed Gastric Peristalsis, *Arch. Roentgen Ray* **16**:242, 1911-1912.

I tried to ascertain under what conditions the antral contraction is of the peristaltic type, and when of the systolic. It seemed logical to suppose that the presence of formed food in the stomach gave rise to the antral systole, and that the purpose of the exceedingly forcible contraction was to help reduce the solids to chyme. The presence of fluid alone in the stomach, on the other hand, necessitated only the usual peristaltic wave to express these contents into the duodenum. However, while work along this line was somewhat suggestive, it was not conclusive. At any rate, both types of waves occur in the normal stomach but the conditions which give rise to one or the other or to their variations are at present undetermined.

Retrograde peristalsis is another phenomenon that occurs. When a solid piece of food, such as an undigested piece of meat, gets into the antrum, a retrograde wave starting at the pylorus forces it back into the body. I have repeatedly produced this retrograde wave by pushing a solid piece of food from the body into the antrum. On one occasion just as I had completed the laparotomy, I noticed a retrograde wave. Palpation revealed an undigested piece of meat in the antrum.

SUMMARY

1. There is both anatomic and experimental evidence for the belief that the gastric wave originates in a nodal center on the lesser curvature at the cardia.

2. There are two main types of gastric waves: (a) the type usually seen with the roentgen ray, in which the wave progresses uninterruptedly from its origin to the pylorus as a peristaltic wave, and (b) the type in which the wave passes downward as a peristaltic wave from its origin to the reentrant angle, and this is followed by a concentric contraction of the antrum as a whole. These waves have been described in dogs, cats, rabbits and man.

3. Variations occur within these types of waves, the chief being the following: (a) The wave passes down over the body reaching the angle and ending there. No antral activity follows. (b) Antral waves may start at the angle and pass to the pylorus as independent waves, and not follow visible waves coming down from above.

4. Retrograde waves may start at the pylorus and run back over the antrum. The presence of a solid body in the antrum may initiate these

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GASTRIC MOTILITY

II. THE CONDUCTION OF THE GASTRIC PERISTALTIC WAVE*

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PROPAGATION OF THE GASTRO PERISTALTIC WAVE

While there is no direct proof that a conduction system exists along the lesser curvature, nevertheless numerous facts tend to show that this curvature is more closely connected with the orderly propagation of gastric peristaltic waves than any other part of the stomach.

In the first place, the structural differences while not significant still are suggestive. The differences in the muscosal folds and in the glands may be passed over as not bearing especially on the present problem. Keith,¹ however, in studying the myenteric plexus found it was well developed along the lesser curvature and in the pyloric division of the stomach. In the fundus and body of the stomach, the fibers of this plexus were much less abundant. Interesting, too, is a further observation of his that stimulation of the lesser curvature near the cardia in a rabbit was followed by the contraction of the muscle at this point. This contraction passed down along the lesser curvature to the angle and then there followed a peristaltic wave which coursed down the antrum to the pylorus.

In his work Alvarez² found that the lesser curvature was the most rhythmic and the most irritable portion of the stomach, with the exception of that area near the cardia which has already been referred to as a possible gastric pacemaker.³ This rhythmicity and irritability grew progressively less as the distance from the cardia increased. From these and other facts he evolved his theory of the gradients, believing that

*From the laboratories of the Department of Surgery, Columbia University College of Physicians and Surgeons. This work is a continuation of Paper I in which the methods used were fully discussed, and in which the origin and character of gastric peristalsis were considered.

1. Keith, Arthur: A New Theory for the Causation of Enterostasis, *Lancet* **2**:371, 1915.

2. Alvarez, W. C.: Differences in Rhythmicity and Tone in Different Parts of the Wall of the Stomach, *Am. J. Physiol.* **40**:585, 1916; Differences in Irritability and Latent Period in Different Parts of the Wall of the Stomach, *Am. J. Physiol.* **41**:320 (Sept.) 1916.

3. Klein, Eugene: Gastric Motility. I, The Origin and Character of Gastric Peristalsis, *Arch. Surg.* **12**:571 (Feb.) 1926.

...no this contraction had occurred near the cardia, it passed downward as a wave from the area of greatest rhythmicity to areas of progressively lesser.

Excisions of portions of the lesser curvature by the surgeon and destruction of areas by such pathologic processes as ulcer give further evidence as to the importance of this part of the stomach for normal motility. An ulcer on the lesser curvature is notoriously associated with delayed gastric motility and with vomiting. And certainly this is not always due, as Haudek⁴ believed, to pylorospasm. For roentgenograms often show the pylorus widely patulous and with a barium shadow nearly as broad as that in the terminal antrum. Schlesinger⁵ recently has described five such cases. In these the emptying time ranged from ten hours to three days in spite of the open pylorus. I have recently observed a patient with an ulcer on the lesser curvature near the cardia in which there was a delay of forty-eight hours in emptying the stomach, and in which the barium shadow in the pyloric ring was always 1 cm. broad. Nor can this delay be ascribed to the toxic effects of the ulcer alone. One of the operations that naturally suggested itself to the surgeon in the treatment of these ulcers was a V-shaped excision of that portion of the lesser curvature containing the ulcer. But very marked disturbances in motility persisted after this operation, and quite often they were worse than they previously had been. A gastro-enterostomy was therefore added to facilitate the emptying, and it was advised to place the stoma high up, if possible proximal to the level of the excision. But many surgeons felt that even here the functional results were poor.

In contradistinction to these findings may be mentioned those of large lesions on the body and greater curvature. With these there is little or no disturbance of gastric motility. Huge sarcomas may occur on the greater curvature. In spite of their size they are usually associated with very little delay in emptying.

Some further very interesting evidence is given by the experiments of Kaplan.⁶ He was studying the effects of some surgical operations on the secretory functions of the stomach. In order to produce an hour-glass stomach, he made an incision through the anterior and posterior walls of the stomach starting on the greater curvature and passing across the body of the stomach to within 2 cm. of the lesser curvature. The anterior and posterior walls of the stomach were then sewed together

4. Haudek, quoted from Schlesinger, E.: Chronische Gastroparese als Folge einer Ulceration auf der kleinen Kurvatur des Magens, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **32**:36, 1920.

5. Schlesinger (Footnote 4).

6. Kaplan: Zur Lehre über den Einfluss der chirurgischen Veränderungen des Magens auf die Verdauungsprozesse, Ztschr. f. physiol. Chem. **87**:313, 1913.

on each side. This, of course, gave him an hour-glass stomach, but it was one of an entirely different character from those occurring in man. For here the initial lesion is usually on or near the lesser curvature, the latter being involved in the pathologic process. In Kaplan's work the lesser curvature was left intact, but there was a complete circular section of almost the rest of the circumference of the stomach. For that reason, his results are especially significant. We have already seen that with lesions of the lesser curvature there is a delay in motility. In Kaplan's work, on the other hand, there was no delay in emptying, much against his expectations. And in one dog in which he had left a channel of only 1 cm. in diameter along the lesser curvature, there was likewise no delay in the emptying of fluids or solids twelve days after the operation.

A curious phenomenon often occurs with these ulcers on the lesser curvature. There is a persistent spasm of the circular muscles at a point opposite the lesion. This contraction, which is in reality of the entire circular segment corresponding to the affected areas on the lesser curvature, has not, I believe, received sufficient attention. It will again be referred to later.

What is the cause for the disturbance in motility with destructive lesions of the lesser curvature? As already intimated, pylorospasm even though it may be proved guilty in some cases, cannot be the cause in all. For, as has been shown, the pylorus is often abnormally relaxed. Schlesinger⁴ believes that the ulcer produces a reflex gastroparesis that affects both the pylorus and the entire stomach. But even granting that this is often true when a pathologic condition, such as an ulcer, causes the lesion on the lesser curvature, we should still have to explain the delay when a portion of the lesser curvature is excised by the surgeon, unless we wish to assume that the resulting scar has the same effect.

The work of Borchers⁷ gives some idea as to what happens to the gastric peristalsis after excision of the lesser curvature. One of the operations that has recently been attempted to effect a permanent cure of gastric ulcers is a resection of the lesser curvature, or "magenstrasse." After this operation had been performed in the cat, a study of the gastric peristalsis by means of the roentgen ray showed that the gastric peristaltic waves were very superficial. No waves nearly as deep as the normal were seen. In a man who had undergone this procedure, an examination five months after the operation showed that the peristaltic waves were about one-half as deep as usual, and after four hours there was still a small barium residue. On the other hand, when the greater

7. Borchers: *Ueber die Resektion der kleinen Kurvature und deren Folgen für Magenform*, Arch. f. klin. Chir. **122**:198, 1922.

curvature was excised in a cat, the waves after operation were seen to be just as deep as before and appeared to be normal. Further, Kaplan⁶ of the St. Petersburg Clinic found that after resection of the fundus and a large part of the greater curvature there was no delay in the emptying of fluids or solids; on the contrary, that evacuation seemed to be more rapid.

It would seem then entirely justifiable to say, in view of these considerations, that the lesser curvature (and for present considerations that portion from the cardia to the angle is meant) is closely related to the propagation of normal gastric peristalsis, and that any severe lesion of this curvature is followed by a disturbance in motility which is due, in part at any rate, to weakening of the peristaltic wave.

CIRCULAR SPASM

We shall next consider the question of circular spasm referred to above. It is well known that an ulcer on the lesser curvature often causes a circular spasm of the entire circular segment in which it is located, so that on the roentgenogram there is an indentation opposite the niche, indicating the ulcer. Westphal⁸ was able to produce a similar phenomenon experimentally. In the exposed stomach of the rabbit he irritated the mucous membrane of different portions of the stomach with the point of a pin. If done on the lesser curvature or in the antrum this caused a spasm of the entire circular segment. On the other hand, if he irritated the mucosa in the lateral walls or fundus of the stomach no such effect was produced. Occasionally only a local contraction occurred about the point of the needle. (Of course one cannot be certain with this technic which of the gastric coats were stimulated, for no doubt the point of the needle often penetrated to the submucosa or even deeper.) I was able to confirm these findings.

Summarizing, then, we may say, first, that the lesser curvature is the most irritable portion of the stomach and that it is the part most intimately connected with the orderly progress of peristalsis; and, second, that irritation of the lesser curvature may lead to a circular contraction of the entire segment. I believe these facts permit the adoption of the following working hypothesis. The impulse of the gastric peristaltic wave starts on the lesser curvature near the cardia. (This was considered in Paper I.³) From here it passes down through what is apparently a conduction system along the lesser curvature.⁹ As the impulse reaches each successive portion of the lesser curvature there follows a contraction of that entire circular segment. In this way there is pro-

⁸ Westphal: *Untersuchungen zur Frage der nervösen Entstehung peptische Ulcera*, Deutsch. Arch. f. klin. Med. **114**:327, 1914.

⁹ The nature of this system—whether it be muscular or nervous—is left for further study.

duced a progressive peristaltic wave passing from above downward. Under normal conditions the contraction of the upper circular segments near the cardia are quite weak; they grow progressively stronger toward the pylorus. The antrum will be considered separately below, as here somewhat different conditions obtain.

This working hypothesis permits an explanation of the disturbances in peristalsis following lesions of the lesser curvature. The effect may vary with the severity of the lesion, whether it be comparatively mild and hence irritative, or severe and destructive and hence paralytic. It emphasizes the conception that the circular muscles of the stomach are arranged in successive segments, not necessarily to be measured in centimeters, but that each portion of the lesser curvature always contracts with the same part of the greater curvature in the course of the peristaltic wave. With a marked destruction in continuity of a portion of the lesser curvature, as by a V excision, there is first produced a break in the conduction system. This apparently causes a weakening of the peristalsis distal to the point of the break and leads to delay in emptying. (Experiments bearing further on this point will be detailed below.) Second, the circular segments from which the lesser curvature has been excised are left without their most irritable portions, those that normally initiate the contractions. These "headless" segments then offer a further barrier to orderly peristalsis. For the stimulus to contract can reach them now only from the adjacent muscular segments. And though it may be possible that after a time some accommodation results, the normal progress of normal peristalsis can never again be attained.¹⁰ Empirical recognition of these facts has led the surgeon after many dismal experience to place a gastro-enterostomy stoma proximal to the level of excision.

CONTROL OF THE ANTRUM

We shall next consider the question of the control of the antrum. It seems likely that on the lesser curvature at the commencement of the antrum, that is, the reentrant angle, a separate nodal center exists, and that in it is initiated the beginning of antral contraction. There is no direct evidence to prove this. No distinct mass of nodal tissue has been described at this point. Nevertheless, some indirect proof is in favor of this conception and it explains well the phenomena of antral contraction.

10. Of course I am aware that other factors aid in emptying, especially in the body and in the fundus. Thus tonus waves of these parts could deliver material to the antrum, and in the "cow-horn" type of stomach tonus waves might be quite effectual agents of emptying. This question will be more fully considered at a later date.

It will be remembered that the stomach is divided into two distinct parts. On the one hand, we have the body and fundus. These act as a reservoir and permit the digestive ferments to act on the food which they hold. On the other hand, we have the antrum whose main function is motor. In a way these divisions are somewhat similar to the division of the heart into auricle and ventricle. And while the analogy does not hold altogether, we are nevertheless justified in inquiring whether, similar to the ventricle, the antrum of the stomach does not possess its own center for the initiation of its contractions. A. A. Berg¹¹ has long felt from clinical observations that this is true.

In the first place, the antrum exhibits a distinct tendency to independent activity. In the observation of the gastric peristalsis in dogs by the method previously detailed,³ it was not uncommon to see this. Thus at times with no waves at all evident in the body, waves would start at the angle and pass down to the pylorus. And often this would be repeated several times. Both Hoffmeister and Schütz¹² and also Wheelon and Thomas¹³ observed the same thing, and on one occasion I saw the following interesting picture: An independent antral contraction of the systolic type³ had occurred. Meanwhile, a peristaltic wave was progressing down the body of the stomach. It reached the beginning of the antrum just as the latter was nearly but not completely relaxed. No antral contraction followed this wave. The next wave coming down from the body was followed by an antral contraction. It seemed that a phenomenon had occurred here parallel to that which takes place in the heart when the impulse from the auricle reaches the ventricle while the latter is in a refractory state due to an extra contraction.

Resection of a triangular area of the lesser curvature at the site of the reentrant angle was performed in two dogs. The opening on the lesser curvature was sewed up in a line parallel with the long axis of the stomach. One dog's stomach was observed by the method previously described³ one month after the operation, and the other six months later. The descriptions follow:

PROTOCOLS

EXPERIMENT 1.—In Dog 1, a triangular excision of the lesser curvature at the level of the incisura was made, Sept. 29, 1920. The wound was sewed up longitudinally. Division of both vagi at the level of the diaphragm was made. October 22, the dog was fed 250 c.c. of milk with 50 gm. of bread.

11. Berg, A. A.: Personal communication to the author.

12. Hoffmeister and Schütz: Ueber die automatischen Bewegungen des Magens, *Arch. f. exper. Path. u. Pharmacol.* **20**:1, 1885.

13. Wheelon, H., and Thomas, J. E.: Observations on the Motility of the Antrum and the Relation of the Pyloric Sphincter to that of the Antrum, *J. Lab. & Clin. Med.* **6**:124 (Dec.) 1920.

Fifteen minutes later, anesthesia was started. A transverse upper abdominal incision was made and the stomach exposed. The scar of the wound in the stomach with a few thin adhesions to it was observed, and a slight but definite indentation of the greater curvature and the anterior wall of the stomach (posterior not visible) running to the scar of the excision. The waves came down the body, starting at the level of the cardia. These were much deeper than the normal in the preantral region. The deepest contraction was at the site of this indentation. There appeared to be a pause for a fraction of a second, and then a peristaltic wave passed down the antrum, at times progressing all the way to the pylorus and at other times not. But all the antral waves were very shallow. No systolic contractions of the antrum were seen.

EXPERIMENT 2.—In Dog 2, a triangular excision of the lesser curvature at the level of the antrum was made, Dec. 1, 1920. The wound was sewed up parallel to the long axis of the stomach. The right vagus nerve was sectioned at the level of the diaphragm. June 2, 1921, the dog was given 500 c.c. of broth containing meat and small bones, and anesthesia was started thirty minutes later. A transverse upper abdominal incision was made. Waves started around the entire circumference of the stomach at the level of the cardia, and travelled downward growing deeper toward the angle. Just beyond the scar they became markedly shallower and often seemed to disappear before reaching the pylorus. At one time a few minutes after the observations were started, some systolic contractions of the antrum were seen. Palpation of the antrum showed the presence in it of some small bones. During the rest of the observation, only the weak peristaltic waves noted above were seen.

These observations then showed that after excision of the angle there was no impairment of the peristalsis proximal to this level; on the contrary, that the strength of the waves seemed somewhat increased in intensity. But there was a definite diminution in the intensity of the waves in the antrum, and, as this occurred in the motor portion of the stomach, it certainly must have interfered with motility. These experiments do not necessarily prove the presence of a nodal center in the angle. But they do show that this portion of the stomach is strongly bound up with the propagation of normal peristalsis in the antrum.

If now an entire circular segment is resected from the stomach, a so-called "sleeve resection," then a remarkable phenomenon results. The resultant scar at the suture line, of course, causes a complete break in the continuity of the intrinsic nerves and of all the muscles. Under these circumstances, the waves proximal to the suture line and distal to this line now occur independently of each other. Thus the body "beats" separately and the antrum "beats" separately. And if one may carry the analogy further, the antrum has established its idio-antral rhythm. Alvarez² showed that the rhythm of the antral musculature was much slower than that of the body. It is natural then to find that the rhythm of the peristalsis in the antrum under the foregoing conditions is slower than the normal peristaltic rate, since the latter is determined by the more highly rhythmic center at the cardia.

Borchers¹⁴ studied the stomach of a cat through a glass window that he had inserted in the abdominal wall after performing a sleeve resection. From his diagram it would seem that the resection was just above the reentrant angle. He found that the waves proximal to the suture line passed down to it at the rate of four per minute. This is the normal rate. Independent waves, on the other hand, starting at the suture line ran down to the pylorus at the rate of two or three per minute.

I studied two dogs following a sleeve resection, one by the method previously described,³ and the other by roentgen ray. In both the waves distal to the suture line occurred independently of those that were proximal.

SUMMARY

The following hypothesis would then seem justified. The gastric wave starts at a nodal center on the lesser curvature near the cardia. The impulse passes down along the lesser curvature. As it reaches each point on the lesser curvature, the entire circular ring at that level contracts and so the peristaltic wave passes down. At the reentrant angle there is a nodal center for the muscular activity of the antrum. Irritating lesions on the lesser curvature may cause a persistent contraction of the circular muscle at the level of irritation. Excision or destruction of a portion of the lesser curvature disturbs the orderly conduction and weakened peristalsis results beyond that level; the impulse reaches the muscle distal to the lesion by passing down along the lateral and greater curvatures. A segmental or sleeve resection is followed by a complete block in conduction, and the establishment of an independent rhythm beyond the level of the suture line.

14. Borchers: Anteil des Nervus Vagi an der motorischen Innervation des Magens im Hinblick auf die operative Therapie von Magenkrankheiten; Studien zur Physiologie und Pathologie der Magen Chirurgie, Beitr. z. klin. Chir. **122**:547, 1921.

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GASTRIC MOTILITY

III. THE MECHANISM OF THE PYLORUS*

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I. RELATION OF ANTRAL CONTRACTION TO THE PYLORIC MECHANISM

Cannon's¹ theory of the acid control of the pylorus has long been accepted by numerous physiologists. Briefly stated—it will be referred to again later—he holds that the pylorus is closed during digestion, that an acidity of 0.2 per cent. on the gastric side brings about its opening, and that the presence of acid in the duodenum effects its closure. The antral waves sweep on repeatedly to the pylorus, but this gateway remains closed until the continued secretion of hydrochloric acid brings up the concentration of the acidity to the level indicated above. The pylorus then opens and the next advancing wave forces the antral contents into the duodenum.

But after studying numerous dogs² by the method previously described, it seemed that this theory could not explain some of the observations that were made. For it became more and more obvious that every wave that progressed to the pylorus forced gastric chyme into the duodenum. Take for instance the following experiment.

PROTOCOL

EXPERIMENT 1.—Dog 1 was fed 375 c.c. of soup containing meat and bones at 1:30 p. m., April 20, 1922. The abdomen was opened by a transverse incision under light ether anesthesia at 2:10 p. m. Retrograde peristalsis in the antrum was immediately noticed. This persisted for five minutes. Palpation revealed a bone in the antrum. This was pushed by hand into the body. After a few minutes waves began coming down from the body, starting opposite the cardia. The rate was four per minute. When the waves reached the angle there was a deep constriction almost cutting the stomach into two parts. There followed a systolic contraction of the entire antrum, involving both circular and longitudinal muscles; but the contraction of the proximal part of the antrum seemed to be a little ahead of the distal. As the antrum con-

* From the laboratories of the Department of Surgery of the Columbia University College of Physicians and Surgeons. The methods used in these studies have been fully discussed in the first paper of this series.

1. Cannon, W. B.: *The Mechanical Factors of Digestion*, New York, 1911, p. 101.

2. Klein, Eugene: *Gastric Motility, I, The Origin and Character of Gastric Peristalsis*, Arch. Surg. **12**:571 (Feb.) 1926.

Every contraction of the antrum was accompanied by a gurgle. Occasionally a contraction started at the angle and was followed by a contraction of the whole antrum. At other times a wave coming down from the body stopped at the angle and was not followed by any contraction beyond. But the typical sequence was as above.

Again and again it was evident from watching all the dogs that every wave that progressed to the pylorus forced contents of the antrum into the duodenum.³

In 1913, Cole⁴ reported at the meeting of the American Medical Association that from a large number of serial roentgen-ray studies in man he was forced to the conclusion that each advancing peristaltic wave propels chyme into the duodenal cap, and that "there is no roentgenological evidence in man of a periodical opening and closing of the pyloric valve independently of each gastric cycle, as described by Cannon." Cannon's work was done with cats. Cole's work was confirmed by McClure, Reynolds and Schwartz,⁵ who also observed the stomachs of normal men through the fluoroscope. They felt, as he did, that the pylorus opened as each and every wave reached the sphincter to permit the passage of chyme into the intestine. And this was true no matter whether fats, carbohydrates or proteins were used in their tests. Reynolds, Lawrence and McClure⁶ later again confirmed this work.

In addition to these facts elicited by the roentgen ray, there is very good experimental evidence pointing in the same direction. Kirchner and Mangold⁷ introduced a balloon into the antrum of the stomach through either a gastric or a duodenal fistula and then recorded the contractions on a smoked drum. They then fed the animals and again recorded the rhythm of the gushes from the duodenal fistula. As both these rhythms were the same, they concluded that every antral contraction was followed by the propulsion of fluid through the pylorus.

3. Contraction of the antrum as a whole is described here, but the same phenomenon was found with the progressive peristaltic wave (character of gastric peristalsis²).

4. Cole, L. G.: The Physiology of the Pylorus, Pileus Ventriculi, and Duodenum as Observed Roentgenographically, J. A. M. A. **61**:762 (Sept. 6) 1913. Motor Phenomena of the Stomach, Pylorus and Cap Observed Roentgenographically, *Ann. Entomol.*, **12**:606 (1916-1917).

5. McClure C. W.; Reynolds, L., and Schwartz, C. O.: On the Behavior of the Pyloric Sphincter in Normal Man, *Arch. Int. Med.* **26**:410 (Oct.) 1920.

6. Reynolds, L., and McClure, C. W.: Motor Phenomena Occurring in Normal Stomach, in the Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically, *Arch. Int. Med.* **29**:1 (Jan.) 1922.

7. Kirchner and Mangold: Die motorische Funktion des Sphincter Pylori und des Antrum Pylori beim Hunde nach querer Durchtrennung des Magens, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **23**:446, 1911.

Luckhardt, Phillips and Carlson,⁸ using a somewhat similar technic, recorded simultaneously the issuing of drops from the duodenal fistula and the contractions of a balloon in the stomach. The fluid was introduced into the stomach through a gastric fistula. Their tracings show that every peristaltic wave was accompanied by a discharge of fluid through the duodenal fistula.

And recently Wheelon and Thomas⁹ have advanced still more direct evidence. Through an incision in the fundus of the stomach, they inserted an apparatus containing a separate balloon for the pylorus and for the antrum, and then recorded the contractions of these parts on a smoked drum. They found that the antral contraction always occurred during a stage of pyloric relaxation. Further, when the pylorus had reached its height of contraction, the antrum in turn had returned to a state of relaxation. They conclude that the activities of the pyloric sphincter are in great part dependent on the activities of the antrum, and that during the digestive processes the impulse to contract in the antrum is propagated into the sphincter. They also state that if acid acts to regulate the pylorus, it must also act in a similar way on the antrum and stomach, for the motility of the antrum determines the motility of the pylorus.

It therefore seems justifiable to conclude from roentgen-ray evidence in animals and in man, and from experimental evidence in animals that the pylorus is normally open at the height of antral contraction, and that every antral contraction is normally followed by the discharge of chyme through the pylorus. Of course, this is at marked variance with the conclusions of Cannon from his studies with cats.

THE FUNCTION OF THE PYLORUS

Krehl,¹⁰ in his admirable book on pathologic physiology, states that the function of the stomach is to prepare food properly for the intestine where the chief phenomena of digestion take place. Three of the more important processes in that preparation are: to fluidify the food, to bring it to the proper reaction, and to approximate its temperature to that of the body. In other words, the stomach effects on its contents if necessary a mechanical, a chemical and a thermal change.

The pylorus is the gateway at the threshold of the intestine. Concerning its mechanism of action there are several theories. All are

8. Luckhardt, A. B.; Phillips, H. T., and Carlson, A. J.: Contributions to the Physiology of the Stomach; the Control of the Pylorus, *Am. J. Physiol.* **50**:57 (Oct.) 1919.

9. Wheelon, H., and Thomas, J. E.: Observations on the Motility of the Antrum and the Relation of the Pyloric Sphincter to that of the Antrum, *J. Lab. & Clin. Med.* **6**:124 (Dec.) 1920.

10. Krehl, L.: *Pathologische Physiologie*. Ed. 11. Leipzig, 1921.

agreed, however, that following the entrance of food into the stomach and during the progress of digestion, it is closed, and that it opens from time to time to permit the onward passage of the gastric chyme into the duodenum. If that is so, it is necessary to assume that some stimuli act at intervals to open it. With normal food, these stimuli must be either (a) chemical, (b) mechanical or (c) thermal. We shall discuss these stimuli in this order.

WE DISCUSS THE CHEMICAL CONTROL OF THE PYLORUS

Effect of Physiologic Dilutions of Acids in the Stomach on the Pylorus.—Among the chief theories of control of the pylorus is one advanced by Cannon.¹ As quoted from his book it is as follows:

The pylorus is tonically closed when food is ingested, and remains closed against recurring pressure. The appearance of acid at the pylorus causes the sphincter to relax. The pressing peristaltic waves now force some of the acid chyme into the duodenum. The acid in the duodenum at once tightens the sphincter against further exit. The same acid also stimulates the flow of alkaline pancreatic juice. Since no inorganic acid is normally present beyond the first centimeters of the small intestine, and since the acid reaction of the contents in this uppermost region is replaced throughout the rest of the small intestine by practically a neutral reaction, the acid chyme must be neutralized soon after its emergence from the stomach. As neutralization proceeds, the stimulus closing the pylorus is weakened; now the acid in the stomach is able again to relax the sphincter. Again the acid goes forth, and immediately closes the passage behind until the duodenal processes have undergone their slower change. And thus repeatedly until the stomach is empty.

The essence of Cannon's theory is, first, that the discharge of food-stuffs is "occasional," and, second, that this irregularity is determined by the time necessary for the acid to reach the proper reaction on the gastric side to open the pylorus, and then by the time necessary to neutralize the acid when it has reached the duodenum.

But there is now a large amount of evidence pointing strongly to the conclusion that the usual chemical reactions in the stomach do not control the pylorus in the manner that Cannon believed. This evidence may be divided into three groups, (a) roentgenologic, (b) clinical and (c) experimental.

(a) In the previous section it was shown that Cole has demonstrated with the aid of the roentgen ray that following the approach of each antral wave to the pylorus chyme was forced through that sphincter. McClure, Reynolds and Schwartz² found the same thing with their fluoroscopic studies, and the experiments of Luckhardt, Phillips and Carlson³ also confirm these findings. This evidence obtained by means of the roentgen ray was shown in the previous section to be confirmed by other methods of experimentation. It is, of course, directly opposed to Cannon's findings of irregularity in the intervals of discharge.

(b) The clinical evidence against the theory is found in the condition of achylia gastrica. Here although there is an absence of acid, the food, whether it be neutral, alkaline or acid, passes on into the duodenum. Cannon¹¹ answered this by saying that it was possible for the organism to adapt itself to abnormal conditions. But that explanation is perhaps not applicable here, for, as will be later shown, food not only leaves the abnormal stomach under these conditions but may also leave the normal stomach in a neutral or alkaline state. And it may do that without any previous preparation whatever, as, for instance, the first time an alkaline meal is administered. This will be discussed in detail later.

(c) The experimental evidence against the theory is as follows: It has long been known that water and egg white may leave the stomach in a neutral condition. That was determined by studies on dogs with duodenal fistulas. Among many others who worked on this problem may be mentioned Hirsch,¹² von Mering,¹³ Moritz,¹⁴ London and Sulima,¹⁵ and Ivy.¹⁶ They are agreed that water given by mouth emerged almost at once from the duodenal fistula. Obviously if an acidity of 0.2 per cent. hydrochloric acid was necessary to open a closed pylorus, this rapid emptying could not occur.

Cannon¹⁷ concedes these facts concerning water and egg white. He cannot, however, make them coincide with his theory and assumes that the presence of these substances is accompanied by a low pyloric tonus that permits of their rapid discharge. Fats, too, do not excite gastric secretion, yet they leave the stomach.

If the pylorus opens only when the acidity reaches a certain level, we would expect that if we were to dilute the gastric contents with a neutral fluid and thus markedly depress the acidity, the emptying would be delayed until the continued secretion of hydrochloric acid had once more brought the reaction up to the proper level. But that does not occur. If fluid is given to an animal at the height of a meal, the fluid very rapidly

11. Cannon (Footnote 1, p. 128).

12. Hirsch: Untersuchungen über den Einfluss von Alkali und Säure auf die motorischen Funktion des Hundemagens, *Centralbl. f. klin. Med.* **14**:73, 1893.

13. Von Mering: Ueber die Funktion des Magens, *Verhandl. d. Cong. f. inn. Med.* **12**:471, 1893; *ibid.* **15**:433, 1897.

14. Moritz: Studien über die motorische Thätigkeit des Magens, *Ztschr. f. Biol.* **24**:565, 1901.

15. London and Sulima: Zur Chemismus der Verdauung im tierischen Körper: Eiweissverdauung im Magendarmkanal, *Ztschr. f. physiol. Chem.* **46**:233, 1905.

16. Ivy, A. C.: Studies in Water Drinking, *Am. J. Physiol.* **46**:420 (July) 1918.

17. Cannon *Physiol.* **2**, p. 131, 1900.

fluid from the stomach. Thus Minckler, after feeding sausage to a dog with a duodenal fistula, found that only 18 c.c. of fluid was recovered from the fistula over a period of one and one-half hours. If 20 c.c. of water was then given, there was very soon a gush of clear fluid from the fistula; this was repeated at intervals. To say that the water passes out through a channel along the lesser curvature does not minimize the force of this argument, for it must pass through the antrum, and can there effect a dilution of the acidity.

That alkaline fluid may leave the normal stomach of man is shown in the work of Spencer, Meyer, Rehfuess and Hawk.¹⁸ When the Rehfuess tube had been passed, they gave their patient 100 c.c. of a 5 per cent. sodium bicarbonate solution. Aspiration of a small quantity for titration every twenty minutes showed that the stomach had emptied itself although the reaction had never become acid.

Then there is the work of McClure, Reynolds and Schwartz.⁵ They kept the reaction in the first portion of the duodenum acid by the injection of hydrochloric acid through a duodenal tube. Nevertheless, under the roentgen ray they could see that each wave in the stomach forced barium over into the duodenum, in spite of the acid there, and when according to Cannon's theory the pylorus should have been tightly closed.

There is then no doubt that food may leave the stomach although no free acid is present in that organ, and this fact is true in both the healthy and the pathologic stomach. As will be remembered, we have assumed that following the entrance of food into the stomach the pylorus closes or, in the words of Cannon, "the pylorus is tonically closed when food is indigested." If the pylorus is closed, and yet, in the absence of free acid, food leaves the stomach, then some other factor must have caused it to open. What that factor may be will be discussed later.

Effects of Abnormal Dilutions of Acids on the Pylorus and on Gastric Peristalsis.—Having discussed the effects of normal concentrations of free acid on the pylorus, I shall now consider the results produced by the higher dilutions and incidentally their effect on gastric motility. It has long been known that acids delay gastric emptying. Hirsch, in 1893, found in his experiments with dogs possessing a duodenal fistula that if distilled water was given by mouth the stomach began to empty itself almost immediately through the fistula and that from 300 to 400 c.c. was discharged in from ten to twenty minutes. Weak alkaline solutions left just as rapidly. On the other hand, if the same quantity of from 0.1 to 0.2 per cent. hydrochloric acid was used, some of the solu-

18. Spencer, W. H.; Meyer, G. P.; Rehfuess, M. E., and Hawk, P. B.: *Direct Evidence as to Effect of Bicarbonates and Its Influence Upon the Gastric and Duodenal Motility*. *Ann. N. Y. Acad. Sci.*, Vol. I, Physiol. 39 (1916), 190.

tion was still present in the stomach at the end of one hour. If the concentration was increased to from 0.3 to 0.5 per cent., then from one-half to two-thirds was still retained after the same interval. If 1 per cent. hydrochloric acid was used, for from five to ten minutes very small quantities entered the duodenum; then expulsion stopped and profuse vomiting followed. Ortner's¹⁹ results with the same method were very similar, and Morse,²⁰ using a somewhat different technic, also found that the rate of the emptying time diminished as the acid concentrations were increased. These results are in accordance with those of other writers, and it seems fairly well established that the higher concentrations of hydrochloric acid delay gastric emptying.

What causes this delay? In his book Cannon²¹ called attention to the fact that two possible factors may be responsible for the discharge of gastric contents: one is the recurring peristaltic wave, and the other the patency of the pylorus. He justly criticized the older workers for not distinguishing between these. In their experiments with duodenal fistulas, if chyme ceased spurting from the fistula following experimental interference, they concluded that the cessation of flow was due to closure of the pylorus. Yet absence of peristalsis could have produced the same result even with an open pylorus. But when working with the duodenal fistulas alone, one cannot say which of these two causes is responsible for the retention of the gastric contents. Cannon, of course, believed that the acid in the duodenum effected a closure of the pylorus until it was neutralized by the intestinal contents. Whether this is so will be fully discussed later. But does the acid produce any effect on the second factor? Does it cause any delay in peristalsis? Not many observations are available to answer this question. Yet those we have seem quite significant.

Among them are those of Schicker,²² who, after ascertaining in fifty-two normal subjects that the average length of time for a wave to travel across the stomach is 20.4 seconds, found that in hyperacidity the interval is 22.5 seconds and in hypo-acidity or achylia 18.5 seconds. In other words, with hyperacidity there is a slowing of the gastric rate. A similar finding was observed by McClure, Reynolds and Schwartz³ in their work with a duodenal tube. With the end of the tube at the antral side of the pyloric sphincter, they introduced 20 c.c. of 1 per cent. sodium bicarbonate solution through it. An acceleration of gastric

19. Ortner: *Ueber die Wirkung von Magensaftkonzentrationen auf die Magenphysiologie*, 168:124, 1917.

20. Morse, W. E.: The Relation of Acid to Gastric Discharge and Duodenal Regulation in the Dog, *Am. J. Physiol.* 41:449, 1916, 1918.

21. Cannon (Footnote 1, p. 99).

22. Schicker: *Reagenzienanalysen des Pankreas und Amylase des Magensaftes*, *Monatsh. Naturg. Med.* 104:366, 1901.

contractions follow immediately, that is, the duration of the wave was decreased from twenty-two seconds to thirteen. Neutralization of the acid present therefore resulted in a marked increase of the rate.

Then Carlson,²³ as a result of his observations on a man with a gastric fistula, reported that "the rhythms of the empty stomach make their appearance whether the stomach mucosa is acid or alkaline in reaction, but that strong acidity or alkalinity caused inhibition." A 0.5 per cent. solution of hydrochloric acid caused greater inhibition than a similar concentration of sodium bicarbonate. There is a slow secretion of gastric juice during the contractions, but a rapid secretion of gastric juice is accompanied by a depression of the contractions. Further observations²⁴ on the same man showed that all acids caused inhibition of the movements and decrease in tonus of the empty stomach when introduced directly into the gastric cavity. The duration of this inhibition was proportionate to the concentration and to the total quantity of acid introduced. Two hundred cubic centimeters of 0.5 per cent. hydrochloric acid solution could cause complete inhibition of the contractions and relaxation of the tonus for from forty to sixty minutes, whereas the same quantity of 0.25 per cent. hydrochloric acid solution usually inhibited for a period of only twenty-five or thirty minutes. Weak concentrations of acid did not inhibit the contractions. He repeated these experiments with normal gastric juice obtained from the patient himself. "The degree of inhibition produced . . . was the same as that caused by an equal quantity of hydrochloric acid of a concentration equal to the free acidity of the gastric juice. It would thus seem that the hydrochloric acid in the gastric juice constitutes the stimulus that leads to the inhibition." Of course, one must remember that the high concentrations mentioned above are not those which normally are present during the course of digestion. And so one of his further findings does not seem contradictory, namely, that the movements of the stomach in digestion are not inhibited by the acids in concentrations equal to that of the gastric juice. During digestion the acid is diluted by the food and other factors which shall be considered later.

But long before any of the foregoing experiments had been done, Ducceschi²⁵ in 1897 obtained similar results. He worked with dogs in which he had produced a gastric fistula. He inserted a balloon through this fistula into the antrum of the stomach. He then injected a 0.1 per cent. solution of hydrochloric acid in the vicinity of the balloon. Marked slowing of the rhythm of the contractions followed. Stronger solutions

²³ Carlson, A. J.: The Character of the Movements of the Empty Stomach in Man, *Am. J. Physiol.* **31**:151, 1912-1913.

²⁴ Carlson, A. J.: Influence of Stimulation of the Gastric Mucosa on the Contractions of the Empty Stomach in Man, *Am. J. Physiol.* **32**:245, 1913.

²⁵ Ducceschi, quoted from Luciani: *Physiologie des Menschen*, Jena, **2**:

caused irregularities in the rhythm and weakening of its activity. If the strength of the acid was still further increased, the contractions ceased or retrograde peristalsis set in. In the cardia, on the other hand, solutions of from 0.1 to 0.5 per cent. seemed to have an augmentor effect.

And Kaplan²⁶ in St. Petersburg, using an entirely different experimental method, came to the same conclusion, namely, that hydrochloric acid stimulates the fundus and inhibits the antrum. It will be remembered, of course, that the chief work of the antrum is motor.

Bearing further on this problem is Experiment 1 outlined above. Fifty cubic centimeters of 1 per cent. hydrochloric acid solution was passed into the stomach of a dog who one hour previously had been fed a full meal. Before the hydrochloric acid was given, the waves were seen by direct observation to pass down the stomach at the rate of four per minute. As the total volume of the meal that had been fed was 750 c.c. there naturally occurred a dilution of the hydrochloric acid. A similar experiment was performed on dogs with an empty stomach.

EXPERIMENT 2. On Day 2, the right and left vagi were stimulated. May 11, 1922.² May 17, the dog received no food. The abdomen was opened, May 18, at 3:20 p. m. One hundred and fifty cubic centimeters of 1 per cent. sodium bicarbonate was immediately passed into the stomach through a tube. Very weak peristaltic waves were noted running all the way down to the pylorus. The stomach was washed at 3:30 p. m. At 3:34 p. m. 150 c.c. of 1 per cent. hydrochloric acid solution was passed into the stomach through a tube. Contractions were seen at once, starting with a constriction at the level of the angle and followed by a systolic contraction of the antrum as a whole. This was repeated twice. Then retrograde waves starting at the pylorus followed. The pylorus contracted first and then a contraction wave ran up to the angle, but the distal portion of the antrum remained very firmly contracted so that the entire antrum was like a hard white cord. Accompanying this retrograde wave was a gush of vomitus. This retrograde wave was repeated three times more, and each time there was a gush of vomitus. The stomach then remained perfectly quiet. The duodenum was not seen as it was overlain by the antrum. A tube was passed into the stomach at 3:43 p. m. and 40 c.c. of dark bile stained fluid was obtained. At 3:44, 1 per cent. sodium hydroxid was passed into the stomach through a tube. Weak peristaltic waves running down to the pylorus were noted. An occasional retrograde wave running from the pylorus to the angle also was seen. No vomiting occurred. At 3:55 the antrum was gently pulled a little to the right. In the duodenum, about 4 cm. from the pylorus, a retrograde wave was seen to start and to run up to the pylorus. At 3:56, 40 c.c. of stomach fluid was obtained through a stomach tube.

Several exceedingly interesting observations not bearing exactly on the facts we are at present discussing may be briefly mentioned. First is the mechanism of the vomiting that occurred when there was a large

26. Kaplan: Zur Lehre über den Einfluss der chirurgischer Veränderungen des Magens auf die Verdauungsprozesse, *Ztschr. f. physiol. Chem.* **87**:313, 1913

the presence of bile in the gastric contents after the withdrawal of the hydrochloric acid showed that there had been a regurgitation of intestinal fluids. This will be referred to again. Finally, the observation of a retrograde peristaltic wave in the small intestine showed that this type of wave may occur there and that intestinal regurgitation is probably to some extent at least the result of such a phenomenon.

But now we are interested in the effects of acid on gastric peristalsis. To summarize the results obtained above: In the first experiment, when 1 per cent. of hydrochloric acid solution was placed in a stomach containing a large amount of food, and hence was diluted, the rate of peristalsis slowed to one-half what it previously had been. In the second experiment, when 1 per cent. hydrochloric acid solution was placed in an empty stomach, three waves carrying the gastric contents toward the duodenum were followed by retrograde waves which caused vomiting, and which were followed by complete cessation of gastric peristalsis.

We have thus far found that acids beyond a certain concentration delay gastric emptying; that at the same time there is a slowing of the gastric peristalsis; that the effect is directly proportional to the concentration and that if the strength of the acid is still further increased there is a cessation of peristalsis and vomiting after some of the material has passed into the duodenum.

The next question of interest is, what site does the hydrochloric acid stimulate to produce this slowing of peristalsis? A great amount of experimental work has been done to ascertain the relationship of chemical stimulation in the duodenum to the pyloric reflex, but little is known as to the effect of such stimulation on gastric peristalsis.

Bearing on the latter problem are some observations of Kirschner and Mangold.⁷ Through a gastric fistula they inserted a balloon connected with a recording apparatus into the antrum of the stomach and traced the antral contractions graphically on a smoked drum. They found that if they injected 20 c.c. of 0.36 per cent. hydrochloric acid solution into the duodenum there was a cessation of antral contractions for two and one-half minutes. If a larger quantity was used, then there was a prolonged inhibition. Eight-tenths per cent. sodium chlorid solution did not have this effect. On the other hand, olive oil also was found to cause inhibition.

Then there is a finding made by Reynolds, Lawrence and McClure,⁸ who by means of the fluoroscope, observed the stomachs of men after a barium meal and with a duodenal tube in situ. In a patient with a duodenal ulcer, cessation of gastric peristalsis followed the pouring of some tenth normal hydrochloric acid into the duodenum through the tube, and at the same time duodenal antiperistaltic waves were set up.

The fact that a duodenal tube was present in the patient should not detract from the value of this observation since it is in entire accord with the experimental evidence outlined above. And also there is further confirmatory data in an earlier paper of McClure, Reynolds and Schwartz.⁵ Here, too, a duodenal tube was in place in the first portion of the duodenum. In two subjects the introduction of twentieth normal hydrochloric acid was followed by duodenal antiperistalsis with either prolonged pylorospasm or almost complete cessation of antral peristalsis. In two other cases following a similar experiment, after a short latent period, there was a marked weakening of the waves. No mention is made as to whether any change in rate was observed.

It would seem that the effects noted above of an irritant concentration of hydrochloric acid, namely, slowing of the gastric peristaltic waves, and perhaps a diminution in their tone, are due to a reflex from the duodenum. It is well known that the duodenal mucosa is far more sensitive than the gastric, and not alone to chemical but also to mechanical stimuli. Although the latter stimuli will be more fully considered later, I may quote from Luckhardt, Phillips and Carlson:⁶ "Vomiting is elicited with the greatest ease by any irritation of the duodenum," and "reflex emesis is certainly more readily elicited from mechanical irritation of the duodenal mucous membrane near the pylorus than from simple irritation of the gastric mucosa. Salivation and retching precede the act." McClure, Reynolds and Schwartz⁵ found that any slight movement of the metal tip in the duodenum caused by pulling on the tube would cause cessation of peristalsis in the stomach. These and other facts to be discussed later add additional weight to the conclusion arrived at above. It will also be remembered that in the experiment on Dog 2 outlined above, in which a solution of 1 per cent. hydrochloric acid was poured into the stomach, there were three movements of expression into the duodenum before vomiting occurred. When Hirsch,¹² in his work with dogs on which he had previously performed a duodenal fistula, passed 1 per cent. hydrochloric acid solution into the stomach through a tube, for from five to ten minutes small quantities entered the duodenum and were expelled through the fistula, then expulsion stopped and profuse vomiting followed. In other words, it would seem that vomiting occurred only after the irritant solutions had reached the duodenum. I would not be prepared to say that still stronger irritation of the gastric mucosa could not set up efforts of expression before any material had entered the duodenum.

We have thus far found that solutions with physiologically non-irritating reactions, whether they are acid, neutral or alkaline, may pass through the pylorus; that if the pylorus is closed, an acid reaction is not necessary to open it; that higher concentrations of acids cause definite delay, and that this delay is in part, at any rate, due to slowing of the

strongly variable, and that even at the concentrations normally encountered there may be a difference of four seconds in the rate of waves in hyperacidity and hypo-acidity, the former being the slower; that the site stimulated by the acid is probably the duodenum; that if very strong acids are used peristalsis is completely inhibited and there may be reverse peristalsis and vomiting. It is possible that at the same time there is some action on the pylorus, that is, that strong acids in the duodenum increase its tone, but, as stated before, no experiments with fistulas alone can be advanced as proof of that contention. The whole mechanism is apparently to protect the duodenum from undue irritation. From that point of view it is hard to see why weak alkalis or neutral solutions should be kept back in the stomach, and one can readily see why the strong acids should be either retained till neutralized or expelled by vomiting.

Effect of Physiologic Concentrations of Acids in the Duodenum on the Pylorus.—Cannon's theory, it will be remembered, is made up of two parts: first, that acids on the gastric side open the pylorus, and, second, that acids on the duodenal side hold it closed. We have seen that acid on the gastric side is not necessary to open the sphincter. We shall now consider whether acid on the duodenal side holds it closed.

The control of the pylorus by acid in the duodenum is in itself widely accepted as a sufficient theory of pyloric control. It is often called the Hirsch-von Mering theory. The mechanical features of this theory will be considered later. In its chemical phase, the acid is believed to close the pylorus when it reaches the duodenum and to hold it until the acid has been neutralized. The sphincter then relaxes and a fresh supply of chyme is again forced into the duodenum; the acid in the chyme again closes the pylorus, and so on. In this country, Spencer, Meyer, Rehfuß and Hawk¹⁸ asserted adherence to the foregoing theory.

It seems very probable that acid on the duodenal side is just as unnecessary for the mechanism of emptying the stomach as it is on the gastric side. And the evidence for this belief is as follows: First, the mechanism of the pylorus functions without acid under the following conditions.

(a) In achylia. Here, of course, there is no acid yet the pylorus opens and closes to permit the passage of chyme. The latter theory can in no way explain this fact. It must be confessed that here is an exception to the rule.

(b) During the early course of digestion. The Rehfuß test meal often shows that free hydrochloric acid does not appear in the gastric contents until fifteen minutes or longer after the ingestion of food. Roentgen-ray observations show that food ingested begins to leave the stomach at once or within a few minutes.⁵ Evidently, therefore, food

material does pass through the functioning pylorus when an acid is present. And we can mention again that even Cannon agreed that the pylorus opens and closes to permit the egress of milk, egg white and fats in the absence of acid.

(c) Spencer, Meyer, Rehfuess and Hawk¹⁸ gave a patient an alkaline solution and then withdrew samples from the stomach at regular intervals to test the reaction; they found that the stomach had emptied itself although the reaction had never become acid.

Second, the experimental introduction of acids directly into the duodenum does not necessarily close the sphincter and keep it so. Of course, hydrochloric acid is an irritant to the duodenum, and, as detailed below, conclusions must be very carefully drawn from its experimental use. Nevertheless, in concentrations higher than it is normally known to exist in the duodenum it does not keep the pylorus closed. Thus,

(a) McClure, Reynolds and Schwartz⁵ found that the injection of acid into the duodenum through a duodenal tube did not prevent the orderly opening and closing of the pylorus and the discharge of barium through it.

(b) The following experiment was performed by me. The method of preparation of the dog was that described in a previous paper.²

EXPERIMENT 3.—Dog 3 was fed 500 c.c. of soup containing meat at 10 p. m. March 2, 1922. A transverse upper abdominal incision was made under light ether anesthesia at 2:15 p. m. Peristalsis was present in the stomach. At 3 p. m. 2 c.c. of 2 per cent. soda bicarbonate solution was injected into the antrum just proximal to the pylorus with a hypodermic syringe and a very fine needle. No effect was seen on the opening and closing of pylorus. At 3:10 p. m. 1 c.c. of 0.3 per cent. hydrochloric acid solution was injected into the duodenum 0.5 cm. beyond the pylorus. No effect on the opening and closing of the pylorus was seen.

In view of all this evidence, it seems justifiable to conclude that the pyloric mechanism may function without the presence of hydrochloric acid in the duodenum. Those who have believed that it is necessary have drawn their chief support from the work of Hirsch,²⁷ von Mering,¹³ Serdjukow²⁸ and Tobler.²⁹ In view of the wide quotation of

27. Hirsch (Footnote 10); Beiträge zur motorischen Funktion des Magens beim Hunde, *Centralbl. f. klin. Med.* **13**:993, 1892; Weitere Beiträge zur motorischen Funktion des Magens nach Besuchen an Hunden mit Darmfisteln, *Centralbl. f. klin. Med.* **14**:377, 1893.

28. Serdjukow: Abstr., *Jahrb. ü. d. Fortschr. d. Physiol.* **8**:214, 1899; Eine der wesentlichen Bedingungen des Durchganges der Speise aus dem Magen in dem Darm, *Arbeiter der Gesellschaft russische Aertzte in St. Petersburg*, August and October, 1899, p. 46.

29. Tobler: Ueber die Eiweissverdauung im Magen, *Ztschr. f. physiol. Chem.* **45**:185, 1905.

their experiments their work will be considered in some detail, and in the order named above, for I feel that their conclusions cannot be applied to the processes of normal digestion.

Some of Hirsch's work has already been outlined. He first showed that organic acids left the stomach slowly and that the higher the concentration, the slower the rate of exit. Although Hirsch stated that he did not believe that the reaction of the gastric contents had any influence on the opening or closing of the pylorus, nevertheless, his experiments are at times not so interpreted. Thus, it is believed that the increased strengths of acid require a longer time for neutralization in the duodenum and hence that the pylorus remains contracted for a longer interval. But surely Hirsch's experiments cannot be said to prove that. As Cannon confessed, they give no answer to the reason why the acids leave slowly—whether this was due to a disturbance in the peristalsis or to the closure of the pylorus. And since it has already been shown that by action on the duodenum there is a reflex slowing of gastric peristalsis and possibly a diminution in gastric tone, that may at least partially account for the slow discharge. Finally, as will again be emphasized, 0.3 per cent., 0.5 per cent. and 1 per cent. hydrochloric acid are not normal concentrations for the duodenum and do not occur there in normal digestion. Any conclusions drawn from their use apply to that strength of acid and not to the strength usually found.

As von Mering's¹³ work is usually referred to in connection with the effect of mechanical stimulation on the intestine, I shall later return to it under that head.

Serdjukow's²⁸ experiments performed in Pawlow's laboratory have been widely mentioned as proof that acid in the duodenum prevents the exit of the gastric contents by keeping the pylorus shut. He poured into the duodenum of a dog with a gastric and duodenal fistula 5 c.c. of pure gastric juice (not gastric contents, which have a much lower acidity) from another dog. This gastric juice was shown to contain 0.52 per cent. hydrochloric acid. Two minutes later, 100 c.c. of 0.25 per cent. sodium bicarbonate solution was passed into the stomach; then every two minutes 5 c.c. of the gastric juice was poured into the duodenum through the fistula. After one and one-quarter hours 95 c.c. of alkaline fluid was still left in the stomach. The inference is that the acid in the duodenum kept the pylorus closed so that none of the gastric contents could emerge. In the first place, this method makes no differentiation between how much of the delay was due to the pylorus and how much to the peristalsis or lack of it in the stomach. Second, what is true of 0.52 per cent. hydrochloric acid need not necessarily be true of acid in the strength normally found in the duodenum. This strength is over twice that normally found even in the stomach contents, which is approximately 0.2 per cent. The subject will be more fully discussed presently.

But to establish once more, the conclusion drawn from this experiment cannot unreservedly be applied to the process of normal digestion, for the strength of the acid he used is far in excess of that which the gastric waves sweep over into the duodenum. And that is very fortunate, for otherwise our stomachs might never empty.

Tobler²⁹ had a dog with a duodenal fistula. Into the duodenum he inserted a balloon and distended this with air so that it would completely block the lumen below the fistula. But alongside the balloon he placed a catheter so that he could inject material through it into the duodenum below the balloon. The animal was fed 100 gm. of finely chopped meat. Spurts of fluid came from the duodenal fistula at intervals of from twelve to twenty seconds, which would correspond to from three to five peristaltic waves per minute. Then if he took the chyme which this dog had expelled through the duodenal fistula on the previous day and which had been preserved on ice, and injected some of it (he does not say how much) from every five to fifteen minutes into the catheter so that it passed into the duodenum below the balloon he obtained the following results:

After every injection there was a cessation of discharge through the duodenal fistula for from three to ten minutes; then the gushes from the fistula began to emerge every three minutes, later from every five to seven minutes, and finally from every ten to twelve minutes. He concludes that the action on the duodenum of the acid in the chyme injected through the catheter was responsible for the closure of the pylorus. The reason the food left so rapidly when the chyme had not been injected was because the acid had no time to stimulate the mucosa of the duodenum and permit it to close the pylorus reflexly. By inference we are therefore led to believe that the second set of results, that is, those in which the chyme was discharged at varying intervals of from three to twelve minutes, reflects the normal process of digestion. Yet such an inference surely is not warranted. In the first place, Tobler states that one must be very careful with the amount of pressure to which the duodenal balloon is distended, for a little too much is sufficient to abolish all discharge from the stomach for a short or longer interval. His injection then is very likely to upset this balance. The presence of such a balloon in the duodenum, which must be so finely adjusted as to pressure, surely places on such a method the burden of proof that the results are applicable to normal digestion. Then again he does not state how much chyme was injected each time through the catheter, and we cannot tell whether it approximated in quantity the amount that is ejected through the pylorus with each peristaltic wave. But following each of these injections the gushes from the stomach stopped for from three to ten minutes. (He says that the

gushes emerged at intervals ranging from ten to twelve minutes. If we accept the evidence given above that every peristaltic wave forces chyme into the duodenum, we have further support to the belief that the unusual conditions under which Tobler did his work gave him these unusually long intervals. For even Cannon¹ (p. 60), who believed that the discharge through the pylorus was at irregular intervals, gives their usual limits as from ten to eighty seconds. There is no other evidence that each discharge of gastric contents into the duodenum is normally followed by an interval of from three to ten minutes. And so Tobler's work, too, cannot be said to prove that acid in the quantities normally found in the duodenum produces a closure of the pylorus and thus regulates the emptying of the stomach.

We may say then of this work that strong acids introduced into the duodenum delay gastric emptying. And this is in entire accord with the work already described showing that high acid concentrations in the stomach delay emptying and that the reflex for this delay is initiated in the duodenum after some of the acid is carried over. It will be remembered that some of the delay was due to slowing and weakening of the peristalsis. And even if at the same time there is a slight spasm of the pylorus in the foregoing experiments, it does not necessarily follow that the same is true when normal reactions and conditions are present.

But what is the usual reaction of hydrochloric acid in the upper part of the duodenum? The evidence seems to show that it is either alkaline or weakly acid. And that does not appear strange, for with an abundance of strong intestinal and pancreatic juices present in the intestine, the neutralization of the free hydrochloric acid carried over from the stomach must consume very little time. Thus, after feeding an animal, the examination of the fluid expelled through a duodenal fistula has in the hands of both Tobler²⁹ and Moritz¹⁴ shown that this material contained no free hydrochloric acid. And in this country Luckhardt, Phillips and Carlson⁸ similarly could demonstrate no free hydrochloric acid. Meyers and McClendon³⁰ ascertained that the hydrogen ion concentration of duodenal contents aspirated at the height of digestion ranged from p_H 3.8 to p_H 7.54. A hydrogen ion concentration of 3.8 is equivalent in terms of hydrochloric acid to a strength of approximately 0.0001 per cent. A hydrogen ion concentration of 7.0 represents neutrality. The reactions they found therefore varied from the acidity indicated above to a very weak alkalinity. Certainly

30. Meyers, F. J., and McClendon, J. F.: Note on the Hydrogen Ion Concentration of the Human Duodenum, *J. Biol. Chem.* **41**:187 (Feb.) 1920.

this strength in no way corresponds to the concentrations used in the experimental work outlined above, and from which conclusions were drawn as to the normal function of this sphincter. It will be remembered, for instance, that Serdjukow used 0.5 per cent. hydrochloric acid solution. We can therefore only conclude from his work that his results obtained for that strength of acid. And the whole would appear as a protective mechanism of the duodenum against high concentrations of acid.

It seems then that we must conclude that during the course of normal digestion, acidity on both the gastric and the duodenal side plays a small part, if any, in the opening and closing of the pylorus.

Summarizing then the effect of chemicals on the pylorus, we may say:

1. The presence of acid on the gastric side is not necessary for the opening of the pylorus.
2. Normal concentrations of acid on the duodenal side do not keep the pylorus closed.
3. Concentrations of acid higher than normal in the stomach cause a slowing of gastric peristalsis, and while this is especially notable in concentrated experimental solutions, it is however also noticeable within the limits found in hyperchlorhydria.
4. Very strong acids cause a complete inhibition of peristalsis, and even reverse peristalsis and vomiting.
5. The site of origin for this reflex is the duodenum.
6. The theory of acid control on both sides of the pylorus (Cannon) or from the duodenum alone does not explain all known facts.

B. EFFECT OF MECHANICAL STIMULI ON THE PYLORUS

Mechanical Stimulation on the Gastric Side.—It has been shown that the action of hydrochloric acid does not adequately explain the control of the sphincter of the pylorus during the course of normal digestion. That leaves as other possible factors thermal and mechanical stimuli. Since thermal stimuli (they will be considered later) must obviously be limited in their influence, mechanical stimulation is left for serious consideration. As in the previous section, the effect of stimulation on the gastric side of the pylorus will be considered first, and then the effect on the duodenal side.

That the contents of the antrum are normally fluid has long been known and conceded, and needs no special comment. Solids are fluidified in the body and fundus by means of ferments, and the constant pressure of these parts aided by the gentle peristalsis forces the fluid or pulpy portion over into the antrum. Here the strong muscular

action helps mechanically to squash the contents. The material forced over into the duodenum is normally fluid. Thus far all agree.

What occurs if perchance a solid portion of food has been carried into the antrum? In four of the dogs studied by me, retrograde peristaltic waves were seen to begin at the pylorus and run up to the reentrant angle, that is, through the entire course of the antrum and up to the body. These were repeated three, four or more times. In each case palpation of the antrum revealed the presence in it of either a bone or a large piece of meat. The peristaltic waves recurred until the solid body had been pushed back into the body of the stomach. In one dog a piece of meat and in another a small bone was pushed by me from the body into the antrum. The normal peristalsis which was going on till then immediately ceased, and retrograde waves commencing at the pylorus forced back the meat and the bone into the body. All these dogs were prepared in the manner previously described.² One-half hour before the observations, they received a meal of broth, meat and small bones totaling one-half liter.

These observations are in agreement with those of Hoffmeister and Schütz.³¹ It will be remembered that their method was to excise the stomach of a dog and to place it in a moist chamber. Some of their dogs had been fed, others had been starved. Occasionally they saw waves commencing at a closed pylorus and running back to the level of the reentrant angle. As these waves were only seen in stomachs that contained coarse food, they concluded that some large particles had found their way into the antrum and were being driven back into the pylorus. They did not, however, actually feel these particles. Over one hundred years ago Magendi,³² too, had reported that any solid bodies carried into the antrum were driven back into the body of the stomach. Von Pfungen³³ had later made a similar observation. Apparently, therefore, a mechanism exists to prevent (for a time at any rate) the passage of solid material into the intestine. That solids can pass over, however, is well known. But they seem to be limited for the most part to nondigestible material, and are probably carried over at the end of digestion when pyloric tone is lowest. On one occasion I followed the progress of a bone through the pylorus. It was a small elongated bone about 1½ inches long. Continuous systolic waves coursed over the stomach, and as each wave reached the bone it was pushed about one eighth of an inch onward. It took fifteen waves to push the bone

31. Hoffmeister and Schütz: Ueber die automatischen Bewegungen des Magens. Arch. f. exper. Path. u. Pharmacol. **20**:1, 1885.

32. Magendi quoted from Luciani: Physiologie des Menschen, Jena **2**:167,

1890.

33. Pfungen: Ueber den Magen. Arch. f. exper. Path. u. Pharmacol. **20**:1, 1885.

through the pylorus. During this time a portion of the food goes, of course, both in the stomach and in the duodenum.

It seems probable (although no work has been done to prove this) that the site for the stimulus of these retrograde waves is the pylorus. Apparently, when the solid particle is carried up against the sphincter the latter closes and retrograde waves which drive it backward are initiated.

This phenomenon is, no doubt, an exceptional occurrence. The influence of the degree of fluidity of the gastric contents on the emptying time of the stomach may, however, be of more importance. As a result of his observation on dogs by means of a duodenal fistula, Hirsch²⁷ first concluded that the fluidity of the stomach contents was one of the most important factors in gastric emptying, but his proofs seem inadequate. Later Moritz,¹⁴ using the same method, reached the same conclusions. Working with water, milk and meat, he showed that pure fluids (water and uncoagulated milk) came out most rapidly; when the milk was coagulated, the rate of discharge was slower. The meat took longest of all to be discharged. Further, if fluid was given the dog while meat was in the stomach, the fluid was expelled rapidly, but the solid portions of meat were retained till either fluidified or changed to a soft pulpy consistency. Cohnheim,³⁴ also using a duodenal fistula, found that finely chopped meat began to leave the stomach in fifteen minutes, and that 50 gm. left the stomach in one hour and thirty-five minutes. If on the other hand, 50 gm. was fed to a dog in lumps from 1 to 2 cm. large, it took two hours and thirty minutes for the stomach to empty itself. More recently, Ortner¹⁹ prepared a thick pulp of charcoal in water and diluted it to suspensions of varying fluid content. These different mixtures were fed to dogs with duodenal fistulas and the time recorded when the first material was discharged through the fistula. He found that the greater the water content, the earlier the discharge through the fistula. Incidentally, all the material discharged was neutral in reaction. He believed that his results spoke very strongly for the theory that fluidification, entirely apart from the reaction and the chemical composition, gave the stimulus for the opening of the pylorus. While that conclusion is entirely possible, it cannot be made with certainty because his method, as before stated, does not distinguish between delay due to the pylorus and that due to slowing of gastric peristalsis. Cannon,³⁵ too, in spite of the great importance he ascribed to the chemical control of the pylorus, believed that the addition of hard particles to the food caused delay in emptying.

34. Cohnheim: *The Physiology and Pathology of the Digestive Tract*, 1908, p. 22.

35. Cannon (*ibid.* p. 121)

We may therefore, say that the state of the material normally discharged through the pylorus is fluid; that a mechanism exists in the antrum or pylorus to hinder the exit of undigested (or unfluidified solids), and that it is probable that the higher the fluid content of the food in the stomach the more rapid its discharge. And in view of the previous discussion of the chemical control of the pylorus, these things are true regardless of the chemical reactions, provided they be within physiologic limits.

Effect on Pylorus of Mechanical Stimulation of the Duodenum.—

The early experimental work to determine the effect on the pylorus of mechanical stimulation of the duodenum is open to the same two faults mentioned in connection with the inquiries concerning chemical control. Thus, first, stimuli were applied that do not occur during normal digestion, and, second, the method did not distinguish between delay due to closure of the pylorus and delay due to cessation of gastric peristalsis.

In 1893 Hirsch²⁷ first called attention to the following fact: If water was given by mouth in an animal with duodenal fistula, it flowed out through the fistula so rapidly that at the end of one-half hour the stomach was always empty. But if he now closed the duodenal fistula and so permitted all the water to pass into the intestine and then repeated the foregoing experiment, at the end of one-half hour appreciable quantities of fluid could still be aspirated from the stomach. And this was also true of an animal in which no fistula had been created. He concluded, therefore, that a reflex from the intestine regulates the emptying of the stomach; that when no duodenal fistula exists, the fluid remains to distend the intestine and a reflex regulates the further discharge. When on the other hand the fluid immediately passed out through the fistula this did not occur and rapid emptying resulted.

A few years later, von Mering¹³ confirmed this. In addition he found that if a dog was given 400 c.c. of water by mouth and immediately following this 300 c.c. of milk was injected over a period of one hour into a duodenal fistula, at the end of the hour only 9 c.c. of fluid was discharged through the fistula, the rest being retained in the stomach. On the other hand, if nothing was injected into the fistula the stomach would be empty in twenty-five minutes. The latter work reminds us of a similar experiment of Serdjukow²⁸ with pure gastric juice (approximately 0.5 per cent. hydrochloric acid), and it is open to the same objections. The injection of ordinary milk in such a manner cannot be said to parallel the ejection of chyme from the stomach by the peristaltic waves. And this is conclusively shown by the fact that at the end of one hour only 9 c.c. of fluid had left the stomach. Then Mar-

baix³⁶ found that if long areas of intestine were filled with fluid through fistulas, the discharge from the stomach was inhibited. Here, again, as Cannon³⁷ points out the conditions are not normal for food is distributed in the intestine in separate short masses. Later Tobler,³⁸ as has already been stated, noticed that if a balloon were inflated in the duodenum, gastric discharge could be completely stopped.

None of these methods prove that the effect produced was really due to closure of the pylorus, although these observers seem to think that this was the cause of the delayed emptying rather than a disturbance of peristalsis. That strong mechanical stimulation of the duodenum does affect gastric peristalsis is shown by the observations of McClure, Reynolds and Schwartz.⁵ During their experiments, previously referred to, they found that pulling back the tip of a duodenal tube from the second and third portion of the duodenum to the pylorus caused a cessation of gastric peristalsis, which lasted in one case one-half hour. These observations were made by means of the fluoroscope.

But strong mechanical stimulation also directly affects the pylorus. Thus, the vigorous mechanical stimulation incident to the introduction of an observation cannula into the duodenum through a duodenal fistula, in an attempt to observe the pylorus, resulted in long continued pylorospasm and vomiting.⁸ And in agreement with the work of other authors, Wheelon and Thomas³⁸ found that an attempt to palpate the lumen of the pylorus with one finger, through a gastric fistula, always led to a firm pylorospasm.

We may say, then, as a result of the foregoing experiments: First, that just as strong chemical stimuli cause delay in gastric emptying, so do powerful mechanical stimuli; second, that this delay is probably due either to closure of the pylorus or to cessation of gastric peristalsis, or both, and it seems natural that these two factors should work together; and third, that such potent mechanical stimuli applied as described above unquestionably have these effects, but that they do not operate under normal circumstances.

One set of observations, however, seems to have an important bearing on normal digestion. This is the work of Hering and Mering¹³ mentioned above in which each showed that the stomach emptied itself more rapidly in dogs in the presence of a duodenal fistula. When the chyme is forced through the pylorus it is passed into the first portion of the duodenum, commonly called the "bulb." This portion acts as a temporary reservoir and its walls are distended by the chyme. When a high duodenal fistula has been performed, the chyme immedi-

36. Mathews: *Le Pylorus Pylorique*, *Le Gall*, 11, 251, 1907.

37. Cannon (Footnote 1, p. 97).

38. Wheelon, H., and Thomas, J. E.: *Rhythmicity of the Pyloric Sphincter*, *Am. J. Physiol.* 54:460 (Jan.) 1921.

passes and through this and no distention of the first part of the duodenum takes place. It seems possible that distention has some influence on the emptying time of the stomach. But whether the reflex effect is exerted on the rate and strength of gastric peristalsis or on the tone of the pylorus, or on both, cannot be stated from the foregoing experiments. We can only say that when the distention occurs the rate of discharge is slower than when it is absent.

In view of the foregoing observations, we may now summarize the effect of mechanical stimuli as follows: If there is material of a fluid or pulpy consistency in the stomach, it is forced into the antrum by the tension of the fundus and body and by the light peristaltic waves of the latter. Every advancing peristaltic wave in the antrum then forces some of this chyme into the duodenum. During the early part of digestion, if a solid piece of food finds its way into the antrum, it is carried back to the body by retrograde peristalsis. During the latter part of digestion, the consistency of the expressed material seems to be thicker, and solid (usually undigestible) substances may be forced through. Further, the chyme is propelled through the pylorus whether its reaction is acid, neutral or alkaline (provided these reactions be within physiologic limits). Strong mechanical stimuli in the duodenum, more marked than those occurring during digestion, unquestionably delay or abolish gastric motility by closure of the pylorus or inhibition of peristalsis or both. But normal stimuli incident to the distention of the duodenal bulb by the chyme may regulate in part the gastric emptying. Whether that effect is on the tone of the pylorus or on the gastric peristalsis, the foregoing experiments do not make clear.

EFFECT OF TEMPERATURE ON THE PYLORUS

The reported effects of temperature on gastric emptying time are somewhat contradictory. Thus, Müller³⁹ found that fluids at body temperature left the stomach most rapidly, while those that were hot or cold left more slowly. Roeder's⁴⁰ results were exactly opposite, the solutions at body temperature being the slowest to leave. It would be exceedingly interesting to determine definitely the effect of temperatures on the tone of the pylorus and on gastric peristalsis. Nevertheless, this effect cannot be of vast importance in the process of normal digestion. For the stomach rapidly brings to body level the temperature of the food that is taken, and any stimulus that would exist because of a variation

³⁹ Müller: *Ueber den Einfluss der Temperatur der Speisen auf die Magen-funktionen*, Zschr. f. diätet. u. physik. Therap. 8:587, 1904.

⁴⁰ Roeder: *Der Beitrag zur Lehre vom Tonus der Mündung des Magens*, Med. Klin. 22:11, 1906.

from that level would at the same time decrease. Cannon, for instance, found that water of 40 degrees C. reached body temperature in the stomach in ten minutes.

OF PROBLEMS ARISING OUT OF CANNON'S THEORY

We shall now pause for a moment to reconsider the questions that have been discussed. We started with an assumption which practically all will accept, namely, that the pylorus is closed following the ingestion of food into the stomach. Then Cannon's theory, the first part of which assumed that acid on the gastric side was necessary to open it, was considered. It was shown, however, that the absence of acid did not prevent the food from leaving, and hence that acid was not necessary for the opening of the pylorus. The second part of the theory was then considered, which like the Hirsch-von Mering theory assumed that acid on the duodenal side controlled the pylorus, the sphincter remaining closed as long as acid was present there, and opening as soon as the acid was neutralized. This theory was likewise found wanting for it would imply that if no acid were present in the duodenum the pylorus would remain continuously open. This is not so, for the pylorus closes in the absence of acid. Further, it was shown that food could leave the stomach even while the reaction in the duodenum was acid. Hence this theory, too, is unsatisfactory. Next, the mechanical theory of regulation from the duodenum was considered. It was found that distention of the duodenum influences the rate of emptying. But no evidence was adduced that in the amounts normally present it controlled the opening and closure of the pylorus. It is possible to believe that distention of the duodenum by the chyme effects the closure of the pylorus, and that its relaxation permits opening. But that has not been proved. And in addition the experiments of Wheelon and Thomas,⁹ already described, showed that the pyloric closure occupies a fixed relation to antral contraction. Evidence presently to be described also tends to show that the peristalsis of the antrum is intimately bound up with the closure of the pylorus, too closely to permit of the belief (just as Wheelon and Thomas found with acids) that mechanical stimulation from the duodenum could effect closure of the pylorus without first acting on the antrum. Nevertheless, it may be that mechanical stimulation of the duodenum influences the tone of the pylorus in the manner to be described later. We may say then that thus far none of the theories are consistent with the facts as we believe them.

When I described in a previous section the character of the peristaltic waves in the dogs I studied,² nothing was stated concerning the pylorus.

⁹ *Gastro-Enter. Chirurgie und Experimentell. u. Klin. med.* 1. exper. Path. u. Pharmacol. **25**:375, 1888, cited by Cannon, *Quart. J. Med.*

The same method that has been described was used. Three sets of observations seem of great importance. First, contraction and relaxation of the pylorus could easily be differentiated. In the former, the muscle was firmly contracted, markedly anemic and white in color. To the touch it was as hard as cartilage. There was no doubt that the lumen was totally obliterated. In the latter, the musculature was definitely relaxed; the color of the musculature was the same pink as that of the relaxed stomach, and the pylorus felt soft. While of course the pyloric lumen could not be visualized, there seemed but little question that it was patent. And that belief was further substantiated by the fact that in some dogs during the entire period of relaxation fluid could be heard and felt being forced through the pylorus. Furthermore, if the pylorus was grasped between the thumb and the forefinger with the one on the gastric and the other on the duodenal side, a lumen of variable size could be felt.

The second fact of importance was the relation of these stages of contraction and relaxation to the gastric peristaltic wave. During normal peristalsis, the contraction occurred only after the peristaltic wave had reached the pylorus. After a regular interval (presently to be considered) the relaxation followed. When no waves were present in the antrum, the pylorus was relaxed. This does not mean that chyme necessarily was passing through, for food does not leave the stomach unless it is pushed out. If Cannon's theory were correct, the pylorus would have been contracted most of the time, and the relaxations would have occurred independently of the peristaltic waves; but, as stated above, unless a peristaltic wave had passed down to the pylorus it remained relaxed. Contraction (except in retrograde peristalsis) did not occur independently of these waves. It was always their culmination.

The third important factor was the time relation of contraction and relaxation. In dogs with four waves to the minute the average length of the contraction, as measured by a stop watch, was from four to five seconds and the average length of the stage of relaxation was from ten to eleven seconds. In other words, the pylorus was firmly closed for from but one quarter to one third of the gastric cycle. For the remainder of the time it was relaxed. That is hardly in agreement with the conception that the pylorus is closed for the larger part of the cycle and opens at intervals to let the food through. It would appear more correct to conceive the pylorus as patent to permit the passage of chyme and closing at regular intervals after each discharge into the duodenum.

These factors lead to the following conception of some of the mechanical conditions incident to digestion. Following the entrance of food into the stomach, the pylorus, which has been relaxed, assumes a state of tone. That is what has usually been referred to as the closure

of the pylorus. Of course, if a circular ring of muscle becomes moderately tonic, and there is nothing within its lumen, its margins will be in contact. In that sense the pylorus may be said to be closed. But normally that state of tone is less than the pressure to which the fluid contents of the antrum are subjected by the advancing peristaltic wave. And so this wave during its progress through the antrum partially overcomes the closure and forces chyme in a continuous stream through the ringlike opening of the pylorus. The size of this ring will depend on the amount of tone of the pylorus on the one hand, and on the pressure created by the peristalsis on the other. During the larger part of the gastric cycle then the pylorus is open, and chyme is being forced through it. It is difficult to say where the tone stimulus to the pylorus arises. But it seems probable that it usually comes after some of the fluid has been passed into the duodenum. Naturally, the amount of tone in the pylorus may vary, but the factors that bring this about have not altogether been determined. We have seen, for instance, that unnatural stimuli, such as strong mechanical irritation, may cause a firm spasm, and this factor may have aided in the slower exit of the strong acids used in some of the experiments outlined above. Also, in normal digestion the acidity and mechanical state of the chyme vary, and they may alter the amount of tone, but the normal stimuli do not cause spasm. It also seems probable that extrinsic impulses through the vagi and sympathetics may vary the amount of the pyloric tone. This is one phase of the activity of the pylorus.

The other phase is closely related to the peristaltic wave. As the peristaltic wave advances down the antrum, its ringlike contraction becomes deeper and deeper until it finally reaches the pylorus. The latter is then contracted to the intensely hard white structure mentioned above. As already stated, the length of this contraction is from one third to one quarter of the cycle. This closure is of a different type from the one described above. Nothing can pass through the pylorus when it takes place. Whether the length of this closure may be influenced by local or distant stimuli, I cannot say. But it appears from watching the waves that the length of the contraction is dependent rather on the rate of peristalsis, and that it consumes a more or less fixed relation to the time of the entire wave. It will also be evident that this firm closure occurs when the pressure in the antrum is lowest (when the advancing wave has reached the pylorus) and when it effectually prevents regurgitation of chyme from the distended duodenal cap.

I would again emphasize, in the first place, the pyloric tone, which the pressure of the chyme in the antrum opens to a diaphragm-like lumen during the larger part of the time, and, second, the firm contractions at the end of the peristaltic waves, alternating with relaxations. If there are no peristaltic waves, these firm contractions do not normally

occur. Under these conditions, if the pressure exerted by the tonicity of the stomach is sufficient to overcome the tone of the pylorus (which may be very low or high, depending on the nature of the foodstuffs and other causes), material may be forced into the duodenum without peristalsis. And on the other hand, if the pressure in the duodenum is greater than the tone of the pylorus and greater than that existing at that particular time in the stomach, then the duodenal contents may be forced back into the stomach. As has already been indicated, the amount of tone of the pyloric sphincter varies during digestion.

The conception that the pylorus remains firmly contracted and opens at intervals not related to the peristaltic waves is, as has already been stated, contrary to the conditions observed. Nor does the theory that the pylorus is firmly closed and opens just before each wave reaches it to permit the passage of chyme, and then directly closes again, accord with the phenomena seen. Further, there are many experimental observations that would tend to confirm the view I have just outlined.

Among these may first be mentioned the work of Boldyreff.⁴² Pawlow⁴³ showed that the strength of the gastric juice as secreted by the glands varied from 0.35 to 0.5 per cent. hydrochloric acid solution. Innumerable observations have confirmed these findings, which are, of course, much higher than those of the acidity of the gastric juice, which ranges between 0.15 and 0.2 per cent. hydrochloric acid solution. How is the reduction in acidity effected? That other factors than dilution by the food or combination with the protein also were at work was shown when a solution of 0.5 per cent. hydrochloric acid was placed in the stomach through a fistula and found after a time to be reduced to an acidity of from 0.15 to 0.2 per cent. hydrochloric acid solution. Evidently, some of the alkaline fluids of the organism had accomplished that. Those that may have brought about this result were the saliva, the bile, the intestinal juice, the pancreatic juice, and an alkaline secretion from the stomach itself. Boldyreff excluded each of these in turn. He then found that the one secretion that was indispensable to proper neutralization was the pancreatic juice. And he concluded that the regurgitation of the latter by retrograde peristalsis brought about the foregoing result.

Boldyreff's conclusion, namely, the regurgitation of pancreatic juice and incidentally of bile into the stomach as a normal occurrence of digestion when the neutralization of acid is necessary, has been confirmed and accepted by many representative workers. Among them may be

42. Boldyreff: The Self Regulation of the Acidity of the Gastric Contents and the Real Acidity of the Gastric Juice, *Quart. J. Exper. Physiol.* **8**:1, 1914.

43. Pawlow: The Work of the Digestive Glands, translation by W. H. Thompson, London, 1910.

mentioned the following. Hicks and Volz⁴⁴ in a series of experiments, using bile as an indicator of intestinal regurgitation (although pancreatic juice may be regurgitated without bile), found that bile was present in the stomach in from 30 to 40 per cent. of the cases. Spencer, Meyer, Rehfuess and Hawk,⁴⁵ working with men who had swallowed a Rehfuess tube, found that if 0.5 per cent. hydrochloric acid solution was introduced into the stomach and samples aspirated through the tube every twenty minutes, the acidity was rapidly reduced, and that as it went down the tryptic values increased. After water was given by mouth, trypsin was found to be present in all aspirated specimens and nearly all contained bile. After a small Ewald meal trypsin was nearly always found to be present. They concluded that regurgitation of the duodenal contents into the stomach is a response to irritation of the duodenum and part of an attempt to render harmless substances that would have an injurious effect on the small intestine. They believe that this phenomenon is a constant accompaniment of gastric digestion. Deutsch and Rürup⁴⁶ recently came to similar conclusions from their studies on forty people. Gross⁴⁶ studied a boy in whom there was an esophageal fistula preventing all saliva from reaching the stomach. The boy was fed through a gastrostomy. Pancreatic ferment could be demonstrated in the stomach at the height of digestion, indicating, of course, pancreatic regurgitation. Morse²⁰ reached similar conclusions with animal experiments.

We may then say with some certainty that duodenal regurgitation is a common occurrence during digestion. If now the pylorus remains tightly contracted, and opens only just before the antral wave reaches it, it is difficult to see how any regurgitation could occur. For it would have to take place against the stream of chyme and at a time when the pressure in the antrum was at its highest. If on the other hand, pyloric tone is moderate or low, retrograde peristalsis or some other form of pressure in the duodenum could easily force over some of the duodenal ferments. This would most likely occur when the pressure on the gastric side was relatively low, that is, either when peristalsis was for a time in abeyance or when the peristaltic wave was quite distant from the pylorus. The firm closure of the pylorus occurs, as was stated, at the termination of the gastric wave.

We shall next consider the work of Cole.⁴ It seems hardly to have received the attention due it. He took serial roentgenograms of a large

44. Hicks and Volz: The Mechanism of the Reflux of Duodenal Contents into the Stomach, *Am. J. Physiol.* **39**:1, 1915

45. Deutsch and Rürup: Ueber den Rückfluss von Pankreassaft in den Magen und die Bestimmung der Salzsaurerestenz des Trypsins, *Deutsch. Arch. f. klin. Med.* **138**:165, 1922.

46. Gross, O.: Ueber der physiologischer Rückfluss von Pankreassaft in den Magen, *Deutsch. Arch. f. klin. Med.* **132**:121 (April) 1920

number of persons at short intervals which placed side by side make almost a moving-picture of the stomach in action. His description of the gastric peristalsis has been outlined above. What concerns us here is that his pictures show that for seven tenths of the gastric cycle the pylorus is open and chyme is being expelled through it. For the remaining three tenths the pylorus is shut. He found, too, that the tone of the pyloric sphincter was greatest during the earliest part of digestion and grew progressively less to the end. The figures mentioned in my experiments, namely, that the pylorus was relaxed for about three fourths of the gastric cycle, agree very closely with those of Cole. Evidently during digestion, when the peristaltic waves are coursing over the stomach, the pylorus is open more of the time than it is shut.

Another group of experiments that may be mentioned are those of Wheelon and Thomas.³⁸ Through an incision in the stomach they inserted a small specially constructed balloon into the pylorus. They used three types. In two of these the pyloric lumen was totally occluded, while in the third a central channel through the balloon permitted the passage of material from the stomach into the intestine. The contractions of the pylorus transmitted by these "pylorographs" were recorded on a drum. They found, after any initial disturbances due to handling had subsided, that there were regularly recurrent waves of contraction, relaxation and quiescence. In one case a roentgenogram was taken at the height of contraction and showed that at that time the pylorus was tightly contracted. Evidently then the summit of each wave is synchronous with pyloric contraction and closure. The time consumed by the contraction averaged from four to five seconds, the relaxation from three to seven seconds, and the quiescent period ranged from five to eight seconds. This makes the duration of a cycle from twelve to twenty seconds. If we remember that the period of contraction was from four to five seconds, this means from one third to one fourth of the cycle and would agree with the figures quoted above. Other exceedingly interesting observations are that the normal tonicity is only sufficient to close the sphincter or to approximate its surfaces against those of a body in the lumen. If that is so it is very logical to assume that any marked increase of pressure on either side, such as occurs with an advancing peristaltic wave, will be sufficient to overcome that tone and to permit the passage of fluid contents. The size of the diaphragm-like opening in the pylorus will depend on the relation between the amount of pressure in the antrum and the amount of tone in the pylorus. And the time of opening also will vary with the relative pressure, so that with a relatively higher tone in the pylorus the moment that the pylorus gives way will be at a later time in the gastric cycle. In that case the open state would be for a shorter length of time. In spite of this, it would appear from the

observations first mentioned and from the rest of the evidence that has been detailed that during periods of peristalsis the pylorus is open for a longer interval than it is closed.

One further set of observations remains to be mentioned. They are those of Luckhardt, Phillips and Carlson.⁸ They performed a duodenostomy and a gastrostomy on their dogs. They introduced a balloon connected to a recording apparatus into the stomach. Either water, an acidified starch paste or a milk peptone mixture also was put into the stomach. A tube was then passed into the duodenostomy opening so that its opening was close to the pylorus. As each drop issued from the tube, it was registered under the tracing of the balloon by a signal magnet. These tracings showed that "the drops issued most abundantly when the constricting ring had reached the pylorus." But the authors do not, it appears to me, emphasize sufficiently that this was not the only time that drops emerged. Their tracings show that as the pressure was rising, that is, as the wave was approaching the pylorus, there also was a discharge of drops. In other words, the pylorus must have been open not only when the constricting ring was close to the pylorus, but also during part of the time it was traveling through the antrum. They further show that gastric contents may pass out through the pylorus in the absence of gastric peristalsis, and owing to a general increase in tonic activity of the musculature as a whole. This is in entire accord with the conception I have postulated, and probably occurs at a time when the pyloric tone is low.

A possible objection that may be advanced is that this patency is not more evident under fluoroscopic examination. I am sure that careful examinations of roentgenograms will very frequently show the patency of the pylorus in the presence of an advancing peristaltic wave in the antrum. And where no shadow is seen at the site of the pylorus, one cannot say that the lumen is closed. I quote from Schlesinger:⁴⁷

It may be very difficult to determine whether the pylorus is open or closed. The observations are made difficult because of the fact that at times only small amounts are expressed which do not cast a visible shadow, or the material expressed may be so completely mixed with substances that permit the roentgen rays to pass through, that even with more profuse emptying no visible shadow arises. The pylorus then appears to be closed when in reality it is open.

In view of these facts, we can see that the problem which confronts us is not so much a study of the factors that are responsible for the opening and closing of the pylorus as a study of the phenomena that influence the gastric emptying time. If pressed for an answer to the

47. Schlesinger, E.: *Die Röntgendiagnostik der Magen und Darmkrankheiten*, Ed. 2, Berlin, 1922, p. 80.

most questions done we would have to say that the pylorus is opened by the increased pressure of the antrum transmitted to the sphincter by its fluid contents, and that the pylorus may be closed in two ways: first, by the approximation of its walls by the tone of the sphincter (which, of course varies in amount) if at the time the pressure on either side is insufficient to overcome this tone, and, second, by the firm contraction that occurs when the peristaltic wave reaches the pylorus.

But since the problem seems to be one largely of pressure relations, we cannot wholly dissociate the behavior of the pylorus from gastric peristalsis and tone. Given the same degree of resistance (that is, the tone of the pyloric sphincter) and a strong propulsive force (that is, the tone of the stomach and the rate and strength of the gastric peristalsis), we will have much more rapid emptying than with the same resistance and a weak propulsive force. The total absence of resistance (a wide open pylorus) will not aid the emptying unless the propulsive force is adequate. On the other hand, the most vigorous peristaltic waves will have great difficulty in overcoming a firm pylorospasm. But under the usual conditions of digestion, the resistance (that is, the tone of the sphincter) is merely sufficient to allow with the increase of pressure in the antrum the passage of a narrow stream of fluid chyme into the intestine, be the reaction of this chyme what it may within normal (nonirritating) limits. The tone of the pylorus exists for that purpose. Normally it only accomplishes the closure of the sphincter when the pressure on the antral or duodenal side is insufficient to overcome it. The decisive closure in the regular cycle of digestion is effected when the peristaltic wave has reached the pylorus. That closure prevents the backward passage of fluid contents from the distended duodenal cap. Studies on the pylorus must distinguish between the effects due to each of these two distinct phases: first, the tone of the sphincter, and second, the gastric cycle consisting of the peristaltic wave and its culmination at the pylorus, producing the closure of that sphincter. This conception is not open to the objections advanced against the other theories, and it is consistent with the known facts of gastric motility and

CONCLUSIONS

1. Acidity on the gastric or duodenal side of the pylorus does not normally control the activity of that sphincter.
2. Fluidity of the chyme in the antrum is the factor of prime importance for its expression.
3. Solid bodies which by chance get into the antrum are carried back into the body by retrograde peristalsis.
4. Each advancing peristaltic wave overcomes the tone of the pylorus and forces some of the chyme into the duodenum, regardless of whether the reaction of the chyme is neutral, acid or alkaline.

5. The period of expression of the chyme during which the pylorus is open occupies a greater part of the gastric cycle than the period in which it is closed; in other words, the pylorus is open for a longer time than it is closed.

6. The pyloric tone normally only keeps the sphincter closed when the pressure on either side is insufficient to overcome it. This is one type of pyloric closure. It is overcome, on the one hand, by each advancing gastric wave, and on the other, may be overcome by retrograde peristalsis in the duodenum resulting in intestinal regurgitation.

7. Firm decisive closure of the pylorus occurs at the termination of each peristaltic wave when the latter has reached the sphincter and after it has forced the chyme into the duodenum. It effectually prevents any regurgitation. The latter closure always occupies the same proportion of time in the gastric cycle.

8. Studies on the pylorus should differentiate between these two types of closure.

EXPERIMENTAL CHRONIC DUODENAL OBSTRUCTION

I. TECHNIC AND PHYSIOLOGY

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There is a growing tendency on the part of clinicians to believe that many obscure and indefinite symptoms are due to the absorption of toxins from the intestinal tract. It is on this hypothesis that high colonic irrigations, bacterial implantations, etc., have been recommended in certain diseases. In addition, some of the more serious conditions, such as pernicious anemia, have been attributed to intestinal intoxication. Though the belief that these hypothetical toxins are produced in the intestinal tract has been prevalent for years, little direct evidence has been brought forward to support the idea. It was in the hope that we might learn something more definite that the following experiments were conducted.

Since the symptoms and diseases that have been attributed to the absorption of toxins from the intestinal tract are characterized by their chronicity, we produced and studied experimental lesions existing for a prolonged period. In our first study¹ we endeavored to confirm the observations of Pawlow and his co-workers,² Fischler³ and others, that dogs with Eck fistulas, kept on an exclusive meat diet, developed symptoms of intoxication. However, in a series of dogs with Eck fistulas which we kept on a similar diet, no such symptoms were observed. It was concluded from these experiments that the occurrence of symptoms was too irregular for systematic study. In addition, the liver function of these dogs was tested according to the dye method described by Rosenthal.⁴ Our results indicated that there was no impairment

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1. Berg, B. N.; Cone, W. V., and Jobling, J. W.: Phenoltetrachlorphthalein Test of Liver Function in Eck Fistula Dogs Kept Upon a Meat Diet. *Proc. Soc. Exper. Biol. and Med.* **23**:81, 1925.

2. Hahn, M.; Massen, O.; Nencki, M., and Pawlow, J.: Die Eck'sche Fistel zwischen der unteren hohlyene und der Pfortader und ihre Folgen für den Organismus, *Arch. f. Exper. Path. u. Pharmacol.* **32**:161 (Sept. 11) 1893.

3. Fischler, F.: Über die Fleischintoxikation bei Tieren mit Eck'scher Fistel, *Deutsche Arch. f. Klin. Med.* **104**:300 (Nov. 7) 1911.

4. Rosenthal, S. M.: An Improved Method for Using Phenoltetrachlorphthalein as a Liver Function Test, *J. Pharmacol. & Exper. Therap.* **19**:385 (June) 1922.

ment in the ability of the liver to remove the disodium salt of phenol-tetrachlorophthalein from the blood stream, although the liver showed the characteristic atrophic and fatty changes that occur following the establishment of an Eck fistula. Subsequently, Mann and Bollman⁵ demonstrated that even large sections of a liver in which an Eck fistula had been established were resected, the elimination of the dye remained within relatively normal limits.

The present series of experiments includes a study of the effects of prolonged stasis in the duodenum, a part of the intestinal tract that is characterized normally by its rapid motility and relative freedom from bacteria. The first two papers of this series deal with the technic, physiology and bacteriology of experimental chronic duodenal obstruction.

During the last few years, numerous clinical observations have been made concerning the relationship between duodenal stasis and systemic disease. A clinical syndrome due to chronic duodenal ileus has been described, and relief of symptoms has been obtained by releasing the mechanical obstruction.⁶ A marked increase in the bacterial content of the duodenum has been noted in cases of pernicious anemia, inflammatory diseases of the biliary tract and various gastric disturbances.⁷ Chronic intestinal obstruction has been found to coexist with some cases of pernicious anemia. An important rôle in the genesis of this disease has been ascribed to the absorption of hematoxins from the intestine associated with a marked increase in the number of bacteria of the small intestine.⁸ Brown and his co-workers⁹ have described a toxic nephritis associated with "duodenal toxemia."

Nothing has appeared in the literature concerning the experimental production of chronic duodenal obstruction, except the work of Koennecke and Meyer.¹⁰ These authors believed that chronic duodenal

5. Mann, E. C., and Bollman, J. L.: An Experimental Study of Reduced Hepatic Function, *Am. J. Physiol.* **76**:179 (March) 1926; *Liver Function Tests*, *Arch. Path. & Lab. Med.* **1**:681 (May) 1926.

6. Higgins, C. C.: Chronic Duodenal Ileus with Report of Fifty-Six Cases, *Arch. Surg.* **13**:1 (July) 1926.

7. Olivet, J.: Bakteriologie des Duodenums, *Klin. Wchnschr.* **5**:307 (Feb. 19) 1926. Löwenberg, W.: Pathologische Bakterienansiedlung im Duodenum und ihre Ursächlichen Faktoren, *Klin. Wchnschr.* **5**:548 (March 26) 1926.

8. Seyderhelm, R.: Die Bedeutung des Dünndarms für die Genese der Perniziösen Anämie, *Klin. Wchnschr.* **3**:568 (April 1) 1924. Seyderhelm, R.; Lehmen, W., and Wichels, P.: Experimentelle Intestinale Perniziöse Anämie beim Hund, *Klin. Wchnschr.* **3**:1439 (Aug. 5) 1924.

9. Brown, G. E.; Eusterman, G. B.; Hartman, H. R., and Rowntree, L. G.: Toxic Nephritis in Pyloric and Duodenal Obstruction, *Arch. Int. Med.* **32**:425 (Sept.) 1923.

10. Koennecke, W., and Meyer, H.: Klinisches und Experimentelles zur Chronischen Duodenalstenose, *Deutsche Ztschr. f. Chir.* **175**:179 (Sept.) 1922.

ileus in man was due to mechanical pressure at the duodenojejunal flexure, and reproduced the condition in dogs by narrowing the lumen of the duodenum with a free, narrow strip of fascia. They fixed the duodenum to the costal arch at the site of the obstruction.

In order to produce conditions that were favorable for the study of the effects of prolonged duodenal stasis in dogs, a method was employed which we subsequently learned was similar to that adopted by Koennecke and Meyer in their work. We believe, however, that our method has the following advantages: By the use of a wide fascial flap attached by a broad pedicle to the posterior sheath of the rectus muscle, instead of a free, narrow, fascial strip, the blood supply of the obstructing band is insured; the obstruction lasts longer, and the danger of the band cutting through the intestine is diminished.

TECHNIC

Under ether anesthesia and with strict asepsis, a right rectus muscle-splitting incision is made. The posterior sheath, including the parietal peritoneum is incised close to the midline, and a rectangular fascial flap, about 4.5 by 6 cm., is made; usually some of the transversalis muscle is included. The size of the flap varies with the diameter of the duodenum. The latter is mobilized, and a segment about 15 cm. from the pylorus is chosen for the site of the obstruction, which varies with the length of the duodenum. An incision equal in size to the width of the flap is made in the mesentery close to the attachment of the duodenum. The flap is pulled through this opening, and five mattress sutures are introduced at the margin and near the base. The distance between the two limbs of the sutures is approximately one and one-half times the diameter of the duodenum. As the sutures are tightened, a closed forceps is introduced between them and the intestine, in order to avoid interference with the blood supply. If at a succeeding exploratory operation the obstruction is deemed inadequate, the fascial band can be tightened by taking a reef in it, a series of interrupted sutures being used. The peritoneum and fascia are closed by a continuous suture and the skin by a subcuticular suture. Silk is used throughout. For the first few days after the establishment of the obstruction, the dogs are kept on a fluid diet after which they are given a liberal amount of cooked chopped meat, bread and bone ash.

EXPERIMENTAL RESULTS

The foregoing method of producing a chronic duodenal obstruction in the dog was successful in twelve of fifteen attempts. Partial occlusion of the duodenum at the site of the obstruction, and dilatation and hypertrophy proximal to the obstruction were found at exploratory laparotomy and at autopsy.

While it was difficult to determine accurately the amount of dilatation due to changes in the tonus of the duodenum, it was found convenient, for tabulation and discussion, to adopt, as a rough measure, the notation given in the accompanying table.

The effects of the partial obstruction on the segment of the duodenum proximal to it as shown in the accompanying table, varied in the different animals. At exploratory operation, in seven dogs a three or four plus dilatation was found from sixty-three to one hundred and twenty-one days after the establishment of the obstruction; in five dogs, a two plus dilatation was present in from thirty-five to one hundred and nineteen days.

Some of the dogs vomited during the first twenty-four hours after the operation. For the first few days, they ate little food. Subsequently, none of them exhibited any objective symptoms except occasional vomiting. Seven dogs lived for periods varying from fifty-nine to 190 days after the obstruction was established. Shortly before death, five developed symptoms of acute ileus; two were killed. Of the seven dogs in this series, four became emaciated. The remaining five are alive, and had been under observation for from 174 to 240 days on September 15.

*Degrees of Dilatation After Obstruction**

Number of Dog	First Exploratory Operation; Days after Obstruction	Degree of Dilatation	Second Exploratory Operation; Days after Obstruction	Degree of Dilatation	Third Exploratory Operation; Days after Obstruction	Degree of Dilatation	Autopsy; Days after Obstruction
8146	17	+	81 T	...	119	+++	190
8246	17	++++	77	++++	121	++++	...
8259	10	+	70 T	...	119	++	...
8265	29	++	108	++	113
8313	35 T	++	73
8314	35	+++	80	+++
8332	49 T	++	70	++
8360	49 T	++	59
8371	47 T	++	80	+++	151
8394	45	++	70	161
8417	30	++++	62	++	84
8418	22 T	+	66	++

* In the table, + represents slight dilatation; ++, moderate dilatation (less than twice the normal diameter); +++, marked dilatation (about twice the normal diameter), and +++++, extreme dilatation (more than twice the normal diameter); T, fascial band tightened at this operation.

The nutrition of these dogs remains unimpaired. No abnormalities of the stools were observed. Complete autopsy observations will be included in a later report.

PHYSIOLOGY

The fluoroscopic observations in clinical cases of duodenal obstruction have been described by Jordan,¹¹ Wheelon,¹² Koennecke and Meyer,¹⁰ Ratkoćzi¹³ and others. In general, they found stasis and reverse motility in the duodenum, gastric and duodenal hyperperistalsis,

11. Jordan, A. C.: The Duodenum and the Appendix in Intestinal Stasis, Brit. M. J. **1**:1225 (June 1) 1912.

12. Wheelon, H.: Observations on Gastric and Duodenal Motility in Duodenal Obstruction, J. A. M. A. **77**:1404 (Oct. 29) 1921.

13. Ratkoćzi, N.: Chronic Stenosis of Duodenum, Am. J. Roentgenol. **12**: 246 (Sept.) 1924.

pyloric insufficiency and reflux into the stomach. Ratkoćzi's description of so-called chronic "intermittent stenosis" of the duodenum contained many features comparable to some of our experimental observations.

In experimental obstruction of the duodenum, the only reports of fluoroscopic examinations that we found recorded were those of Koennecke and Meyer,¹⁰ who correlated their clinical with their experimental observations. They stressed the hypermotility of the stomach and duodenum in the presence of experimental stenosis and noted that section of the vagus had only a transitory effect on gastric tonus after the obstruction had been established for a prolonged period. Occasionally, they identified deep peristaltic waves which originated in the stomach and progressed over the duodenum in contrast to the to-and-fro movements of the duodenum. However, they did not recognize any rhythmic relation between antral, pyloric and duodenal activity.

METHOD

In order to study the degree of stasis and alterations in the peristaltic activity of the stomach and the duodenum in the presence of a prolonged subacute obstruction of the latter, fluoroscopic examinations were made with the aid of an opaque meal. Seven dogs were examined. Three separate series of observations were made on each dog, with intervals of from one to two weeks between each examination. The obstructions had existed from 115 to 173 days when the first fluoroscopic observations were made. Eight ounces of a suspension of barium sulphate was given to the dogs by stomach tube. They received no food eighteen hours before the examination. Observations were made in the following manner: immediately, at the end of one hour, two hours, three and one-half hours, and five hours (in only two series). The fixation of the duodenum to the anterior abdominal wall facilitated accurate study, and the site of the obstruction was readily recognized. There was no evidence of kinking below the obstruction.

MOTILITY

In the normal dog, fluoroscopic examination is unsatisfactory for the observation of the motor relationship between the duodenum, pyloric sphincter and antrum. However, in the presence of an obstruction of the duodenum, we found that the accentuation of the contractions and the delayed motility enabled us to distinguish, simultaneously, the activity of each. We observed a cycle that was suggestive of one described by Wheelon and Thomas¹⁴ in the normal dog, but which differed in certain respects.

As soon as enough barium had passed through the pylorus the duodenum appeared as a long, sausage-shaped structure, limited above by the pyloric sphincter and below by the obstruction. The degree of dilatation varied; in some dogs the duodenum was twenty times its normal

14. Wheelon, H., and Thomas, J. E. Observations on the Motility of the Duodenum and the Relation of Duodenal Activity to that of the Pars Pylorica. *Am. J. Physiol.* 59:72 (Feb.) 1922.

slow in others, the dilatation was less pronounced. Variations also occurred in the same dog at different observations. These changes were probably the result of alterations in tonus; because of this it was considered futile to compare roentgenographic appearances with gross dilatation observed at exploration. However, there seemed to be some correlation between the latter and the degree of stasis. This is discussed in detail under the heading of stasis and dilatation.

After the filling of the duodenum, the following cycle was observed in six of the seven dogs that were examined: A deep peristaltic contraction appeared in the antrum and progressed toward the pylorus; sometimes the entire antrum appeared to contract at one time instead of in the form of a peristaltic wave. As the wave approached the pylorus, the latter opened and barium passed through into the duodenum; then the pylorus closed, and the contraction traversed the duodenum, causing a marked bulge in the latter as it approached the obstruction. Immediately after this there appeared a definite to-and-fro motion of the mass of barium in the duodenum (apparently independent of the antrum), the result of deep contractions that traveled alternately toward the obstruction and then toward the pylorus. During reverse movements, the bulb was momentarily distended, especially when the sphincter was closed. At some observations, the sphincter was open, and reflux into the antrum occurred. After four or five of these alternating contractions, peristaltic activity in the antrum appeared anew, and the rhythmic cycle was repeated. In the interval between contractions, the antrum appeared to be inactive and usually only partly filled with barium. Sometimes it was empty, possibly because of a tonic contraction of the so-called "sphincter antri pylorici"¹⁵ or of the antrum itself. Similarly, the duodenum at times did not contain barium; this may have been caused by a tonic contraction of either the pyloric sphincter or of the duodenum. In such cases, the cycle could not be distinguished. In one dog, in which there was apparently slight obstruction, the cycle was not observed. It will be noticed throughout the remainder of the study that this dog was practically normal.

Sometimes, when the lower or middle portion of the duodenum was tonically contracted, the cycle could be identified only in the upper duodenum and bulb. When reflux into the antrum was marked, the duodenum and antrum appeared to be continuous, and it was more difficult to distinguish the cycle. It seemed as though the antral peristaltic wave spent itself more rapidly than usual, because of increased resistance from irregular contractions in the duodenum. At many observations, the barium was propelled beyond the obstruction in jets, which followed only duodenal contractions of antral origin. At other times,

15. Hofmeister, F., and Schütz, E.: Über die Automatischen Bewegungen des Magens. *Arch. f. Exper. Path. u. Pharmacol.* **20**:1 (Oct. 6) 1886.

the barium appeared below the obstruction in a continuous thin stream, throughout the cycle.

When the antrum and duodenum were well outlined, the rhythmic motor activity described above was recognized with few exceptions at the immediate, the one-hour and the two-hour observations and less often at the end of three and one-half hours. At the five-hour period, the duodenum usually appeared flaccid and dilated, and was traversed by feeble, irregular contractions. Occasionally, moderately deep alternating contractions persisted. No barium was observed passing the site of the obstruction at this time. This may have been because of the fact that the amount propelled beyond the obstruction was too small to be detected fluoroscopically.

The body and fundus of the stomach were often separated from the antrum by a deep contraction band. The antrum maintained a regular rhythm, which seemed to be independent of activity in the cardiac portion of the stomach. In the latter, peristalsis appeared in the form of "ripples," although occasionally, when the waves were sufficiently deep, they were observed traversing the antrum. As a rule, however, they were too shallow for any relationship between them and the antral contractions to be disclosed fluoroscopically.

COMMENT

According to Wheelon and Thomas,¹⁴ a rhythmic cycle that follows the "law of the intestine"¹⁶ exists between the antrum, pyloric sphincter and the duodenum. In the normal dog, as soon as the antral peristaltic wave has reached the sphincter, the antrum begins to relax and remains relaxed during the sphincteric and duodenal contractions. The cycle terminates with the reappearance of an antral contraction. Similarly, in chronic duodenal obstruction there was a positive and negative phase of antral activity. Immediately after the wave of contraction passed from the antrum to the sphincter and duodenum, the antrum relaxed and remained inactive during four or five independent secondary contractions in the duodenum. The cycle ended with the reappearance of an antral contraction. However, the duodenum appeared to contract continuously without a phase of relaxation which corresponded to that of the antrum. In the latter, the negative phase seemed to be prolonged and the rate of rhythmic contraction slow.

The accentuated contractions and the reverse motility of the duodenum were due, probably, to changes in tonus associated with the dilatation and to abnormal stimuli arising at the obstruction. The irregular activity of the duodenum represented either *exaggerated* ~~normal~~ *normal* contractions¹⁴ or independent peristaltic and retroperistaltic waves. The

¹⁶ Bayliss, W. M., and Starling, E. H.: *The Movement and Innervation of the Small Intestine*, J. Physiol. **24**:99 (May 11) 1899.

delayed motility, especially at the five-hour observation, may be explained by alterations in the "gradient," as described by Alvarez.¹⁷

The tonicity of the pyloric sphincter varied during the phase of independent duodenal activity. At some observations, it appeared contracted; at others, it allowed reflux into the antrum. The activity of the sphincter can be modified by duodenal motility during the negative phase of the antrum.¹⁴ The prolonged reverse motility of the obstructed duodenum probably induced marked alterations in the pyloric sphincter, which, however, were not recognized by the fluoroscope.

The site of origin of the antral peristaltic contraction, which appeared to be independent of activity in the fundus and body of the stomach, requires finer methods of study for a more accurate interpretation. Recently, Klein¹⁸ found that, normally, antral contractions may originate either at a nodal center near the cardia, along the lesser curvature of the stomach, or independently, at a separate nodal center at the reentrant angle.

STASIS

In all of the dogs, there was a delay in the passage of the barium through the duodenum proximal to the site of the obstruction. The emptying time and the amount of residue varied. In four dogs, there was a persistent residue at the end of five hours; in two dogs, the duodenum was filled with barium at one five-hour observation, but was empty at another. In one dog, the duodenum was always empty at the one-hour observation. This dog was referred to earlier as having practically no delay in motility.

More pronounced variations occurred in the emptying time of the stomach. However, marked irregularities also exist normally. At one observation of a normal, fasting dog, the stomach was empty at the end of one hour; at another observation of the same dog, a gastric residue was still present at the end of three hours. Wheelon and Thomas¹⁴ noted similar variations in the dog and in man. Bloomfield and Keefer,¹⁹ employing a different method, recently reported wide differences in the motility of the normal stomach in man.

In chronic duodenal obstruction, the stomach always contained barium at the one-hour observation, except in the dog in which the obstruction apparently had little effect. In one series, four dogs had five-hour gastric residues. In another series none of the dogs had

17. Alvarez, W. C.: *The Mechanics of the Digestive Tract*, New York, Paul B. Hoeber, Inc. 1922

18. Klein, E.: Gastric Motility: Origin and Character of Gastric Peristalsis, *Arch. Surg.* **12**:571 (Feb.) 1926

19. Bloomfield, A. L., and Keefer, C. S.: Clinical Physiology of the Stomach: Simultaneous Quantitative Observations on Gastric Secretory Volume, Acidity and Motility, *Arch. Int. Med.* **38**:145 (Aug.) 1926

residues at the end of five hours. It was interesting to note that, in the latter series, six dogs had marked stasis in the duodenum.

The pylorus usually allowed the passage of barium from the stomach to the duodenum at the immediate observation. Sometimes from five to fifteen minutes elapsed before any barium appeared in the duodenum. At the obstruction, after a short delay, barium usually began to enter the distal duodenum and the upper jejunum in varying amounts. However, in two dogs there was a marked delay of one-half hour and two hours, respectively. The latter dog developed symptoms of acute ileus the day after this observation. At the five-hour observation, except for the duodenal and gastric residues noted, the barium was in the large intestine and occasionally in the lower ileum also.

In one dog, the outline of a large oval mass was observed in the greatly dilated duodenum just above the site of the obstruction. It was in the same situation at the three series of observations. However, it did not obstruct the lumen of the duodenum completely, the barium passing around it in a thin film. The mass was probably a large hair ball (a similar one was found in the dilated duodenum of another dog that came to autopsy). This dog is in excellent condition and has evidenced no obstructive symptoms up to the present time.

STASIS AND DILATATION

In spite of the fact that the fluoroscopic examinations were started from forty-two to sixty-four days after the last exploratory operation, the notes made at the explorations concerning the degree of dilatation of the duodenum coincided well with the degree of stasis observed roentgenologically. In five dogs, in which a marked dilatation of the duodenum (three or four plus) had been noted, a corresponding five-hour residue existed. In one dog, although only a moderate dilatation (two plus) had been observed, barium was still present in the duodenum at the end of five hours. This was the dog that had the mass in the duodenum described above; the added obstruction probably developed after the last exploratory investigation. In the other dog in which only a moderate dilatation had been observed (two plus), the duodenum was empty at the end of one hour.

Too much emphasis must not be placed on such observations, however, because the degree of stasis varies and is determined by many other factors besides the mere gross dilatation of the duodenum; the degree of the obstruction, the amount of compensatory hypertrophy and tonus of the duodenal musculature, the tonus of the pyloric sphincter, gastric motility, psychic factors, and the character of the food must all be considered. It is unfortunate that earlier fluoroscopic examinations were not made for comparative studies. Keenbeck and Meyer¹² found a five-hour residue in the duodenum of a dog in which the obstruction had existed five weeks.

COMMENT

It is interesting to note that, despite active reverse motility in the duodenum, often with an open pylorus, vomiting occurred only twice during the fluoroscopic examinations, and infrequently during the entire period of observation. The symptoms associated with retention and reverse motility in the duodenum have been discussed from a clinical point of view by Wheelon²⁰ and others. In a series of seventy-four cases reported by Wheelon, only eight presented a history of vomiting. Clinically, chronic duodenal ileus is characterized by many subjective symptoms such as headache, dizziness, nausea, "biliousness," and a sense of fulness in the epigastrium.

However, since such subjective symptoms cannot be elicited experimentally, it is impossible to draw any analogies. None of the dogs developed the objective nervous symptoms usually associated with intoxication.

In view of the marked alterations in the duodenum associated with chronic obstruction, the possible relationship of such changes to infections of the biliary tract and alterations in the regulation of the flow of bile must be considered. Carlson,²¹ Burget²² and Kodama²³ have emphasized the possible importance of the tonus of the duodenal musculature in the closure of the ampullar end of the common duct. Preliminary studies of the dogs of this series indicate that the gallbladder bile in more than 50 per cent contained large numbers of organisms of intestinal origin.

CONCLUSIONS

1. A simple method of producing chronic duodenal obstruction in the dog is described.
2. Dilatation and hypertrophy of the duodenum developed above the obstruction.
3. Fluoroscopic examinations confirmed the existence of prolonged duodenal stasis.
4. Alterations in the contractions of the antrum, the pyloric sphincter and the duodenum occurred, and a rhythmic cycle between the three was observed.
5. Except for emaciation in some of the dogs and occasional vomiting, there were no symptoms of intoxication.

20. Wheelon, H.: Symptoms Associated with Duodenal Retention and Reverse Motility, *J. A. M. A.* **86**:326 (Jan. 30) 1926.

21. Carlson, A. J.: Physiology of the Liver, *J. A. M. A.* **85**:1468 (Nov. 7) 1925.

22. Burget, G. E.: The Regulation of the Flow of Bile, *Am. J. Physiol.* **74**:583 (Nov.) 1925.

23. Kodama, S.: A Model to Simulate the Mechanism of Emptying of the Gallbladder, *Am. J. Physiol.* **77**:385 (July) 1926.

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EXPERIMENTAL CHRONIC DUODENAL OBSTRUCTION

II. BACTERIOLOGY *

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In the search for a possible origin of some of the chronic and sub-acute illnesses of men in which there seems to be clinical evidence of a low grade intoxication, attention has recently been focused on the gastro-intestinal tract. In a previous paper, two of us with Cone¹ reported the failure to obtain evidence of absorption of toxic substances from the normal intestine in dogs that had Eck fistulas and that were kept on a meat diet. We were then led to study the effect after a partial obstruction of the intestine. It became evident at once that it would be necessary, before going further, to study the altered anatomy and physiology as well as the changes in the bacterial content of the intestine resulting from this procedure. In the paper immediately preceding this,² we have endeavored to indicate certain of the anatomic and physiologic alterations. In the present paper we shall present our observations with regard to the bacteriologic changes.

HISTORICAL

Ever since Billroth³ made the observation that the meconium of new-born babes was free from bacteria, and that micro-organisms made their appearance in the first yellow stools, bacteriologists and clinicians have been interested in the bacterial content of the intestine. Their interest has led to extensive researches to determine, if possible, the significance of the countless organisms which grow in the alimentary canal of animals and man. Their behavior during the normal physiologic

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1. Berg, B. N.; Cone, W. V., and Jobling, J. W.: Phenoltetrachlorphthalein Test of Liver Function in Eck Fistula Dogs Kept upon a Meat Diet, *Proc. Soc. Exper. Biol. and Med.* **23**:81, 1925.

2. Berg, B. N.; Meloney, F. L., and Jobling, J. W.: Experimental Chronic Duodenal Obstruction. I. Technic and Physiology, *Arch. Surg.*

3. Billroth, T.: Untersuchungen über Vegetationsformen von Coccobacteria Septica, Ser. 94, Berlin, 1874. (Quoted by Cushing and Livingood: *Johns Hopkins Hosp. Rep.* **9**:543, 1900).

function of the digestive tract is doubtless the outcome of age-long mutual adaptation which has resulted in the establishment of a relative equilibrium. The host survives with comparatively little evidence of injury to itself, and the bacteria maintain their species with relatively unimportant variation in numbers. Studies of this so-called normal relationship are interesting, but the disease phenomena which result from the invasion of the body by these bacteria after injuries to or the absorption of their products following altered physiologic processes of the alimentary canal makes fascinating problems for research.

Surgeons observed long ago that wounds of the stomach and upper intestine were not always followed by peritonitis as were wounds of the lower intestine. They found that operations in the upper regions could be performed with impunity, while sections of the lower portions were attended with grave risk of death. On the other hand, occlusions of the intestine produced profound symptoms of intoxication which were greater and more rapidly fatal when they were in the upper levels than when they were lower down. Cushing and Livingood,⁴ were stimulated by the former observations to attempt a study of the bacteria from the human stomach, duodenum and jejunum, taking specimens as opportunity afforded at the time of or after operations on the alimentary canal and from fecal fistulas, for the most part in pathologic conditions. They also studied the intestinal fluid at various levels in rabbits and dogs. Old as it is, their work has many points of interest in the present discussion, and reference to it merits some detail. They were struck by the irregularity of their results, and concluded that there were no peculiar or stable flora in the intestine except perhaps *Bacillus coli* in the lower intestine. They found "no marked differences between the colonies on aerobic and anaerobic plates" but frequently saw bacteria in smears, which they could not cultivate. They confirmed the observations of previous research workers that there were many more bacteria in the lower than in the upper intestine. They noted, however, that the number at all levels decreased greatly after starvation, and that the lower limb of a fecal fistula became sterile. They concluded that bacteria were ingested with food and water and were killed in large numbers in the stomach if the food were delayed there for a time. Viable bacteria were therefore scanty in the duodenum but multiplied rapidly during their passage through the small intestine. After the passage of the chyme, if no more food was taken, the intestine tended to become amicrobic. They recommended the abstinence from food preliminary to operations

4. Cushing, H., and Livingood, L. E.: Experimental and Surgical Notes upon the Bacteriology of the Upper Portion of the Alimentary Canal, with Observations on the Establishment There of an Amicrobic State as a Preliminary to Operative Procedures on the Stomach and Small Intestine, Johns Hopkins Hospital Rep. 9:543, 1900.

on the stomach and duodenum and presented cases to prove that the suggestion was a worthy one.

Since the publication of these observations, a number of authors have reported work which confirms many of the observations of Cushing and Livingood. The duodenal bucket has afforded to many observers, Libert,⁵ Hoefert,⁶ and others, the opportunity to study the bacteria of the duodenum under normal and disease conditions. There is general uniformity of opinion that bacteria are found in the upper intestine in relatively small numbers under normal conditions of the stomach and biliary tract, but that the organisms in the mouth and pharynx and those contaminating the food and drink are found in great numbers if the gastric acidity is low, or if the biliary tract is diseased. In 1918 and 1919, Kendall,⁷ and Torrey,⁸ and others since that time, found that changes in diet modify the flora of the intestine, certain types of bacteria being favored by certain food elements and inhibited by others. Rettger and Cheplin⁹ asserted that certain bacteria may be introduced into the intestine and maintain an existence for a time, retarding the development of other bacteria which are considered harmful. Dragstedt and his co-workers¹⁰ confirmed the observation that diet modifies the flora of the intestine, but stated that if intestinal stasis or acute intestinal obstruction is produced, no matter what the predominating types were before, the putrefactive bacteria promptly become predominant and may be responsible for the intoxication found in those conditions.

One is surprised to find that many of the reports in the literature do not mention that anaerobic cultures have been made; others state that there was no difference between the aerobic and anaerobic cultures. Many authors noted that bacteria frequently were seen in smears which could not be cultivated. Cushing and Livingood,⁴ particularly, described a large bacillus which was often present but which would not grow. It is possible that these were anaerobes which could not develop in the degree of anaerobiosis attained by these workers. Others have appreciated the importance of anaerobic cultures.

5. Libert, Edmond: *Le tubage duodenal; Ses applications au diagnostic et au traitement. Considerations sur la flore duodénale normale et pathologique*. Paris, 1924.

6. Hoefert, Bruno: *Ueber Bacterienbefunde im Duodenalsaft von Gesunden und Kranken*, *Ztschr. f. klin. Med.* **92**:221-223 (Nov.) 1921.

7. Kendall, A. I.: *Recent Developments in Intestinal Bacteriology*, *Am. J. M. Sc.* **156**:157-172 (Aug.) 1918.

8. Torrey, J. C.: *The Regulation of the Intestinal Flora of Dogs through Diet*, *J. M. Research* **39**:415-447 (Jan.) 1919.

9. Rettger, L. F., and Cheplin, H. A.: *A Treatise on the Transformation of the Intestinal Flora*, New Haven, Yale University Press, 1921.

10. Dragstedt, L. R.; Cannon, P. R., and Dragstedt, C. A.: *Factors Controlling the Intestinal Bacteria. The Effect of Acute Obstruction and Stasis on Bacterial Types*, *J. Infec. Dis.* **31**:209-214 (Sept.) 1922.

With the idea that the anaerobic organisms might be significant in certain types of intestinal obstruction, we have made both aerobic and anaerobic cultures in the present study. We have also attempted to correlate our observations with the anatomic and certain of the physiologic conditions revealed at subsequent operations.

TECHNIC

In a previous paper, we have described the technic of partial duodenal obstruction in dogs.² The principle is to use a living sheet or band of parietal peritoneum and posterior sheath of the rectus from the abdominal wall and to diminish the lumen of the gut to considerable degree without obstructing it completely. All food was withheld from the animals for thirty-six hours before operation, and water was withheld for sixteen hours. Specimens of duodenal fluid were obtained by stripping the gut approximately 10 cm. from the pylorus and clamping 5 cm. of the duodenum thus stripped between two rubber protected clamps. We estimated that this left approximately 0.5 milliliter of fluid, held largely between the crypts and folds of the gut. With a syringe and a no. 16 Luer needle, this segment of the gut was washed thoroughly with 5 milliliters of the supernatant fluid from 0.2 per cent dextrose cooked meat medium from which the air had been driven by boiling. The needle hole was closed with a purse string suture previously laid and tied as the needle was withdrawn. One milliliter of this fluid was then planted into a tube of dextrose cooked meat medium, and 0.1 milliliter was transferred to the first of a series of twelve tubes, each containing 0.9 milliliter of the supernatant broth. After thorough shaking, 0.1 milliliter was transferred from the first to the second tube and so on through the series. Thus each tube contained approximately one tenth of the bacteria present in the preceding tube. Allowing for experimental error, the number of organisms present could be estimated within one digit. The fluid withdrawn after washing the segment of the gut represented an approximate dilution of from 1-10. In the small tubes, the dilutions ranged from one to one hundred to one to ten trillion. The tubes were then incubated under strict anaerobic conditions in a McIntosh and Fildes jar.¹¹ In this medium under these conditions, both aerobes and anaerobes develop satisfactorily. After twenty-four hours culture, streaks were made on 5 per cent sheep blood agar plates from the tubes showing growth. One set of plates was incubated aerobically and another set anaerobically. Smears from the broth indicated to what dilution each type of organism had been distributed. On the next day, the plates were examined to confirm the observations in the tubes. Individual colonies could then be fished for further identification. From these tubes and plates, an estimate could be made of the number of viable organisms of each type in the original duodenal fluid. For example, let us say that five of the small tubes showed growth. In the first tube, gram-positive cocci, large gram-positive bacilli and small gram-negative bacilli were found. Gram-positive and gram-negative bacilli were present in the second and third tubes, but only gram-positive bacilli in the fourth and fifth. The anaerobic plates made from the first of these tubes showed the typical large double zoned colonies of *B. welchii*, small gray colonies containing gram-negative bacilli and small colonies of cocci which turned green on exposure to the air. The aerobic plate from the first tube showed only large

11. McIntosh, J., and Fildes, P.: A New Apparatus for the Isolation and Cultivation of Anaerobic Microorganisms, *Lancet*. 1:768-770 (April 8) 1916.

gray colonies of gram-negative bacilli and small green colonies of cocci. The anaerobic plates from the second and third tubes developed typical *B. welchii* colonies, and small gray colonies of gram-negative bacilli. The aerobic plates from these tubes showed only large gray colonies of gram-negative bacilli. The anaerobic plates from the fourth and fifth tubes again showed *B. welchii* colonies, while the aerobic plates did not show any growth. From such observations one could estimate that there were between 10 and 100 aerobic gram-positive cocci, between 1,000 and 10,000 aerobic gram-negative bacilli and between 100,000 and 1,000,000 anaerobic gram-positive bacilli in one cubic centimeter of the original fluid.

EXPERIMENTAL RESULTS

In a preliminary series, the obstruction was made just above the ileocecal valve. In eleven dogs, specimens of fluid were taken from the duodenum, lower jejunum and lower ileum just above the occlusion. The results in this series were unsatisfactory, since all but one dog died as a result of the procedure. The causes of death included general peritonitis, acute obstruction and pneumonia. However, certain of the preliminary results are of interest and are included here, particularly the ante-obstruction observations of bacteria in the duodenum. The results from these eleven normal dogs were added to the figures from the fourteen dogs of a later series in which the obstruction was placed at the lower end of the duodenum. Thus we obtained cultures from the duodenum of twenty-five normal animals.

In the early experiments the organisms found in the lower intestine belonged to many types which could not be classified, and a complete analysis was not practical. However, the bacteria in the duodenal fluid were few in number and variety and in almost all cases could be isolated and identified. It soon became evident that there were three principal bacterial groups, namely, aerobic gram-negative bacilli of the *B. coli* group, aerobic gram-positive cocci of the nonhemolytic or green streptococcus group and anaerobic gram-positive bacilli of the *B. welchii* group. Other organisms rarely found were *B. proteus*, *Staphylococcus aureus* and *albus*, *B. sporogenes* and certain gram-positive aerobic bacilli. In the later experiments, no attempt was made to classify the organisms further than to put them into one of these three groups. The results are given in table 1.

A survey of these results brings out certain points of more or less significance. First, let us take the normal series. In only one of the twenty-five (4 per cent) was the duodenum sterile. In seven, the Welch bacilli existed alone. In three, the streptococci and in one the colon bacilli existed alone. In six, all three forms were found. The cocci were present in fourteen and absent in eleven. The gram-negative bacilli were present in eleven and absent in fourteen. The gram-positive anaerobic bacilli were present in seventeen and absent in eight. It is seen that the gram-positive anaerobic bacillus was the type most con-

sistently found in the duodenum of the dogs of our series. If anaerobic cultures had not been made, 32 per cent instead of 4 per cent would have been considered sterile.

One is struck by the high counts in four of this series of normal dogs. We cannot explain this inconsistency except to suggest that in some way or other there was a high intake of bacteria just before operation. There is a possibility that the dogs were fed, although the caretakers deny this, and no food was found in the stomach at operation. It is significant that these animals were all operated on within a single week. It is possible that they were a poorly nourished group. With these exceptions, the bacterial count of the normal duodenum of our dogs was low.

TABLE 1.—Results of Duodenal Obstruction in Dogs.

No.	Laboratory No.	Before			Day P.O.	Degree of Obstruction	Second Operation			Day P.O.	Degree of Obstruction	Third Operation			Day P.O.	Degree of Obstruction	Fourth Operation		
		ber	+C	-B	+B		+C	-B	+B			+C	-B	+B			+C	-B	+B
1	8981	0	1	1
2	8987	0	1	1
3	8968	0	1	1
4	8101	0	0	1
5	8164	0	0	1
6	8165	4	1	0
7	8119	0	0	1
8	8126	1	1	1
9	8135	1	6	1
10	8147	1	0	0
11	8160	1	1	0
12	8100	0	0	0	17
13	8191	0	0	2	17	++++	5	5	4	77	++++	4	4	4	121	++++	5	5	4
14	8201	1	0	0
15	8201	1	0	0
16	8269	1	1	1	16	+	1	0	2	70	++	4	4	4	119	++	3	3	1
17	8265	0	0	0	10	+	0	2	6	108	+	5	6	4
18	8313	0	1	0	35	++	4	5
19	8314	0	0	2	35	+++	0	4	4	80	+++	2	3	2
20	8292	0	0	1	49	++	5	5	6	70	+++	5	6	5
21	8291	0	0	1
22	8291	5	7	7	49	++	5	7	6	59	++++	3	3	6
23	8291	7	7	45	++	6	6	4	80	+++	7	7	4
24	8334	..	3	45	++	6	9	7	79	+++	2	5	5
25	8417	..	1	30	++++	5	0	5	63	++++	0	5	4
26	8418	0	6	3	65	++	5	6	4

In this table and in table 2, 0 indicates no growth; 1, from 1 to 100 per cubic centimeters; 2, from 10 to 100 per cubic centimeter; 3, from 100 to 1,000 per cubic centimeter; 4, from 1,000 to 10,000 per cubic centimeter; 5, from 10,000 to 100,000 per cubic centimeter, etc. + indicates slight dilatation; ++, moderate dilatation; +++, marked dilatation; +++++, extreme dilatation. +C indicates gram-positive cocci; -B, gram-negative bacilli; +B, gram-positive bacilli. Figures in the "Days P.O." column are the number of days after the production of an obstruction was present in the duodenum.

Eleven of these animals and one other which did not have an ante-obstruction culture taken, were reexamined after a partial obstruction had existed in degree varying from slight to extensive for from ten to forty-nine days.

In none of the twelve examinations was the gut found sterile. In only one did a single type exist alone, and that was the gram-positive anaerobic bacillus. In six, all three forms were found. The cocci were present in nine and absent in three. The gram-negative bacilli were

present in ten and absent in two. The gram-positive anaerobic bacilli were present in eleven and absent in one. It is seen that there was a striking increase in all types. In general, the greatest increase in numbers was found when the greatest dilatation was present, but this was not invariable. Fluoroscopic examinations as reported in the previous paper revealed the fact that the delay in emptying almost always corresponded closely to the degree of dilatation.

It is seen that certain types were present after obstruction which were not found before, and vice versa; also that the type predominating before had no certainty of predominating afterward. In general, the gram-negative bacilli increased more than the others but not strikingly, as Dragstedt¹⁰ reported for his cases of acute obstruction.

When little obstruction was present, it was increased slightly at the time of the second operation by tightening the band. When eleven of the animals were examined a third time, from fifty-nine to 108 days after obstruction, it was found again that in no case was the duodenum sterile, and in no instance did a single type exist alone. In ten, all three types were present. The cocci were present in ten and absent in one. The gram-negative bacilli and the gram-positive anaerobic bacilli were present in all instances. It is seen also that there was a general increase in the number of all three types. Again, it is seen that the predominating type changed, and that the gram-negative bacilli gained more than the others. In every instance but one, the degree of dilatation either had been maintained or had increased.

Three animals were examined a fourth time, from 119 to 121 days after obstruction, and again the gut was not sterile in any instance. In all of the cases all three types were present, but the numbers were less than at the time of the preceding examination. The gram-negative bacilli, however, maintained their numbers better than either of the others. The degree of dilatation was somewhat increased.

In eleven of the twelve dogs having a third or fourth examination, cultures were made not only of the fluid in the gut above the obstruction but also of that from the lower jejunum for comparison. The gut immediately below the obstruction frequently was found collapsed, and in the region of the middle of the gut this condition was also often present. In seven of these cases the number of organisms in the lower jejunum was less than in the duodenum above the obstruction. In three of these seven, certain types which were present above the obstruction were absent below. These results are shown in table 2.

At the same time, cultures were made of bile taken from the gall-bladder by aspiration without primary dilution. In six of the eleven cases, organisms were found in considerable numbers. These observations are of great interest and warrant a more extensive study.

COMMENT

Certain of our observations corroborate the work of previous observers. Aerobic bacteria were present in the majority of duodenums of our normal dogs for a considerable length of time after the passage of food through the duodenum. With anaerobic organisms also considered, it was found that the duodenum was rarely sterile. The viable bacteria were enormously increased in number after chronic or partial obstruction of the duodenum which produces a delay in the passage of intestinal contents and some degree of distention and hypertrophy of the gut above the obstruction. This relative increase in the viable organisms in the stripped gut was striking, but attention should be called to the fact that the dilated lumen filled with material made the actual increase even greater. The amount of fluid probably did not vary more than three or four times the estimated quantity in any case, while the number of bacteria per milliliter increased thousands of times. This increase is probably caused by a multiplication of the bacteria in

TABLE 2.—*Results of Duodenal Obstruction in Dogs Shown After A Third or Fourth Examination*

Number	Laboratory Number	Number of Operations	Day of Obstruction	Degree of Obstructions	Above			Below		
					+C	-B	+B	+C	-B	+B
1	8190	4	119	+++	5	5	4	5	5	2
2	8191	4	121	++++	1	1	3	5	7	7
3	8200	4	119	++	3	3	1	5	5	0
4	8205	3	108	+-	3	6	4	1	7	7
5	8314	3	80	+++	2	3	2	1	5	3
6	8332	3	70	+++	5	6	5	1	5	4
7	8360	3	59	++++	3	3	6	0	0	2
8	8361	3	80	+++	7	7	4	3	4	3
9	8364	3	79	+++	2	5	5	2	2	1
10	8417	3	63	++++	0	5	4	0	0	0
11	8418	3	66	++	5	6	4	4	7	6

the duodenum. Any delay of food in the stomach favors a great destruction of bacteria, but when the food mass has passed the pylorus, it comes in contact with the duodenal fluids which have a much weaker antiseptic action.

The great variability of the flora from time to time in animals with duodenal obstruction, with a predominance of now one and now another type, suggests that the bacteria are constantly changing, and that this variation depends on the intake and survival of the different types of bacteria rather than on the variance of the local conditions. But there is some evidence that the conditions tend to favor the predominance of the gram-negative organisms. When bacteria are growing together in large numbers, the question of their interaction becomes an important one. In a number of instances there seemed to be an inhibition of the growth in the test tube of the gram-positive anaerobic bacilli cultured from our animals by the gram-positive aerobic cocci. The symbiosis

and antagonism of bacteria are questions which have been studied greatly but have not been elucidated. Castellani¹² has recently made some simple and convincing experiments which indicate definitely that certain organisms when growing together may perform certain functions which neither could accomplish alone.

The fact that down in the middle of the intestine the viable bacteria were frequently less than above the obstruction suggests that, with the passage of the food mass and a collapse of the tube, there may be some antiseptic action by the gut mucosa on the bacteria in immediate contact with it. It is probable that many bacteria penetrating the wall are destroyed. Radel,¹³ tried but failed to demonstrate any growth-inhibiting substance in extracts or emulsions of the stomach or intestinal wall, and suggested that whatever the antiseptic action, it must be a function of living cells. This may be something of the same nature as that which prevents digestion of the living mucosa by the digestive fluids.

Our observations with regard to the presence of bacteria in the bile of certain of the dogs with duodenal obstruction is of considerable importance and will be continued and carefully controlled. A report will be made in a subsequent paper.

It has been found repeatedly by many observers that the lower gut is in contact with billions of organisms, while the duodenum normally is not. The question arises whether the lower gut normally has any resistance to the action or invasion of these organisms which the duodenum has not. May such resistance be developed by the duodenum after prolonged contact with them? Although the cases are too few to draw conclusions, there is a suggestion, in the falling off in numbers of bacteria in the examinations made in the later stages of obstruction, that this feature of the problem may well merit investigation. One is reminded of the intestinal immunity results of Besredka in this connection.¹⁴

SUMMARY

1. In the duodenum of our dogs, bacteria were normally present. In 70 per cent of cases anaerobic gram-positive bacilli of the *B. welchii* type were found. In 50 per cent, varieties of the nonhemolytic strepto-

12. Castellani, A.: The Importance of Symbiosis or Close Association of Different Species of Organism in the Production of Certain Biochemical Phenomena and in the Causation of Certain Diseases and Certain Symptoms of Diseases, J. A. M. A. **87**:15-22 (July 3) 1926.

13. Radel, F. W.: Sind in der Dünndarmschleimhaut Bakterienwachstum Hemmende Stoffe (Bakteriostanine) nachweisbar? Ztschr. f. d. ges. exper. Med. **48**:658-670, 1926.

14. Besredka, A.: Immunisation Locale Pansements Spécifiques, Paris, Masson & Cie., 1925.

cocci group and in 40 per cent members of the *B. coli* group were present. Thus the anaerobic gram-positive bacilli were the most consistent but were not invariably present.

2. After partial obstruction of the duodenum, these organisms were found in enormously increased numbers varying with the degree of obstruction and the extent of dilatation of the intestine above the obstruction. The greatest increase in numbers was with the bacilli of the *B. coli* group, but there was no striking difference between this and the other types.

3. This increase was maintained for a considerable period, but in some cases there was a decrease later, even though the obstruction persisted.

4. The flora of the duodenum in any particular animal was not constant, now one and now another type predominating.

5. The gut immediately below the obstruction was usually more or less collapsed. In more than half of the cases of this series, there were fewer viable organisms in the lower jejunum far below the obstruction than in the gut just above the obstruction.

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